INTRATHECAL MORPHINE OR CLONIDINE FOR POSTOPERATIVE ANALGESIA IN PATIENTS UNDERGOING URETHROPLASTY – A COMPARISON

A dissertation submitted to the Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the requirement for the degree of M.D Anaesthesiology (Branch X) Examination to be held in April 2016.

CERTIFICATE

This is to certify that this dissertation titled “Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.” is an original research work done by Dr. Geetha Bhavani Gullipalli, Reg.no.201420356, in partial fulfillment of the requirements for the M.D Anesthesiology Examination Branch X of the Tamil Nadu Dr. M.G.R Medical University to be held in April 2016.

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Principal,

Christian Medical College, Vellore.

DECLARATION

I Geetha Bhavani Gullipalli, do hereby declare that this dissertation titled “Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.” is a genuine record of research work done by me under the supervision of Dr. Tony Thomson Chandy, Professor, Dept. of Anesthesiology, Christian Medical College, Vellore and has not been previously formed the basis for the award of any degree , diploma, fellowship or other similar title of any University or institution.

Vellore, Dr. Geetha Bhavani Gullipalli

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January 09, 2015

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Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty - a comparison.
Dr. Geetha Bhavani Gullipalli, PG Registrar, Dr. Tony Thomson Chandy, Dr. Divya Jacob, Anaesthesiology, Ms. Tunny Sebastian, Biostatistics, CMC, Vellore.

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Dear Dr. Geetha Bhavani Gullipalli,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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Dear Dr. Geetha Bhavani Gullipalli,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison." on November 26th 2014.

The Committee reviewed the following documents:

1. IRB Application Format
2. Curriculum Vitae' of Drs. GeethaBhavaniGullipalli, Tony Thomson Chandy, Divya Jacob, Ms. Tunny Sebastian
3. Proforma
4. Permission Letter
5. Informed Consent Form (English, Tamil Hindi, Telugu, Bengali)
6. Information Sheet (English, Tamil Hindi, Telugu, Bengali)
7. No of documents 1-6

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: https://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

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The trial need to be registered with Clinical Trial Registry India (CTRI) http://ctri.nic.in before commencing.

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Audio – Visual consent needs to be taken. Use the hospital Insurance Scheme – contact Mr. Samuel Abraham, Personnel Department, CMC, Vellore for a legal opinion and document regarding the Hospital Insurance Scheme and be downloaded in the CMC Intranet / Internet Webpage link: http://172.16.11.136/Research/ > CMC Research > Insurance Coverage Scheme – Clinical Trials within CMC > October 2014 – October 2015.

Fluid Grant Allocation:

A sum of 6,820/- INR (Rupee Six Thousand Eight Hundred and Twenty only) will be granted for 1 year.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

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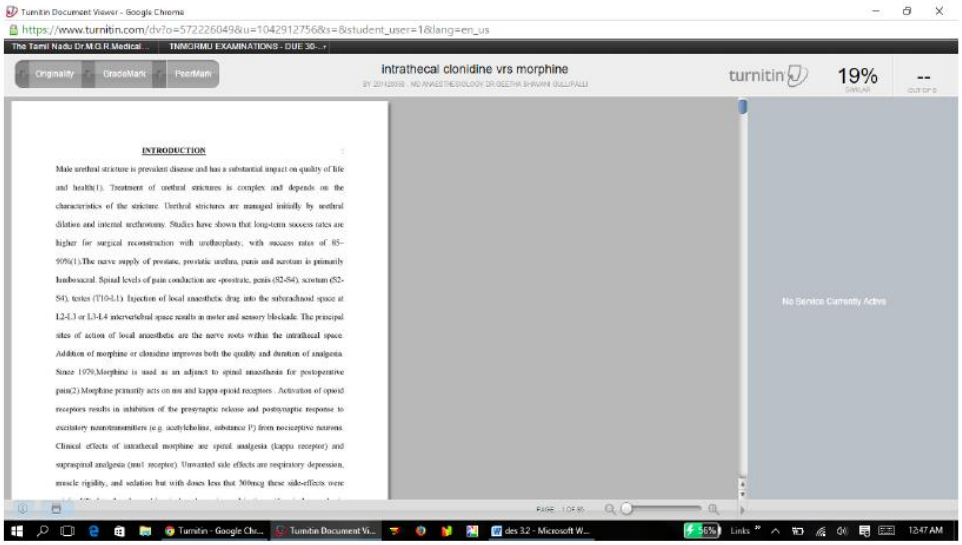
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INTRODUCTION
Male urethral stricture is prevalent disease and has a substantial impact on quality of life and health(1). Treatment of urethral strictures is complex and depends on the characteristics of the stricture. Urethral strictures are managed initially by urethral dilation and internal urethrotomy. Studies have shown that long-term success rates are higher for surgical reconstruction with urethroplasty, with success rates of 85-90%(13).The nerve supply of prostate, prostatic urethra, penis and scrotum is primarily lumbosacral. Spinal levels of pain conduction are -prostrate, penis (S2-S4), scrotum (S2-S4), testes (T10-L1). Injection of local anaesthetic drug into the subarachnoid space at L2-L3 or L3-L4 intervertebral space results in motor and sensory blockade. The principal sites of action of local anaesthetic are the nerve roots within the intrathecal space. Addition of morphine or clonidine improves both the quality and duration of analgesia. Since 1979,Morphine is used as an adjunct to spinal anaesthesia for postoperative pain(2).Morphine primarily acts on mu and kappa-opioid receptors . Activation of opioid receptors results in inhibition of the presynaptic release and postsynaptic response to excitatory neurotransmitters (e.g. acetylcholine, substance P) from nociceptive neurons. Clinical effects of intrathecal morphine are spinal analgesia (kappa receptor) and supraspinal analgesia (mu1 receptor). Unwanted side effects are respiratory depression, muscle rigidity, and sedation but with doses less that 300mcg these side-effects were
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I express my sincere and heartfelt gratitude to Dr. Tony Thomson Chandy, Professor, Department of Anesthesiology, Christian Medical College for his encouragement, meticulous support and tremendous guidance during the study.

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I am extremely grateful to My Colleagues and Anaesthesia Technicians for their help during the study.

I acknowledge the valuable help from Miss.Tunny Sebastian, Lecturer, Department of Biostatistics, Christian Medical College, and Vellore in designing the study and for analyzing the study results.

I am extremely grateful to all my patients who agreed to participate in this study.

ABSTRACT

TITLE OF THE ABSTRACT: Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.

BACKGROUND:

Urethroplasty, a surgical repair is attempted as corrective measure in the male urethra for urethral stricture after conservative and non-surgical methods does not produce the desired patient satisfaction. The perineal region is an area supplied with a profuse sensory nervous supply. Surgical procedures to the region may produce severe pain in the post-operative period.

OBJECTIVES:

To compare the effectiveness of intrathecal morphine and clonidine for postoperative analgesia and their effect on postoperative sedation, nausea and vomiting and time to mobilization in patients undergoing urethroplasty surgery.

METHODS:

Type of study: Prospective Randomized Controlled double blinded study.

After approval by the institutional review board, total of 46, ASA grade I and II patients were enrolled and randomly assigned to two groups after informed consent over a period of six months. Group A (23 patients) received morphine (3mcg/kg body wt.) and Group B (21 patients) received clonidine (1mcg/kg body wt.) intrathecal injection prior to

general anaesthesia. Heart rate, systolic, diastolic and mean blood pressures were monitored at regular intervals. During the post- operative period VAS score, Ramsay sedation score, PONV were assessed at 0,1,2,4,8,12 and 24hrs.

RESULTS:

Intrathecal clonidine (1µgm/kg body weight) provides effective hemodynamic stability during laryngoscopy than intrathecal morphine (3µgm/kg body weight).The average duration of surgery(median 4hrs), the analgesic effect of clonidine is comparable to the analgesic effect of morphine in the early postoperative period, i.e., first 12hrs post surgery and morphine has prolonged analgesic effect. Though statistically insignificant (p value >0.05) clonidine has prolonged analgesic effect on buccal mucosa than morphine. There is no significant sedative effect and PONV in both groups.

CONCLUSION:

Clonidine had significantly better intraoperative hemodynamic response to sympathetic response to painful stimulation during intubation and skin incision. Morphine provided a moderately longer duration of pain relief compared to clonidine. The prolonged analgesic effect on buccal mucosa could possible because of the central alpha 2 agonist activity of clonidine.

KEY WORDS:

Intrathecal clonidine, intrathecal morphine, urethroplasty, post-operative pain, sedation, PONV, buccal pain

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INTRODUCTION

Male urethral stricture is prevalent disease and has a substantial impact on quality of life and health(1). Treatment of urethral strictures is complex and depends on the characteristics of the stricture. Urethral strictures are managed initially by urethral dilation and internal urethrotomy. Studies have shown that long-term success rates are higher for surgical reconstruction with urethroplasty, with success rates of 85–90%(1).The nerve supply of prostate, prostatic urethra, penis and scrotum is primarily lumbosacral. Spinal levels of pain conduction are -prostrate, penis (S2-S4), scrotum (S2-S4), testes (T10-L1). Injection of local anaesthetic drug into the subarachnoid space at L2-L3 or L3-L4 intervertebral space results in motor and sensory blockade. The principal sites of action of local anaesthetic are the nerve roots within the intrathecal space. Addition of morphine or clonidine improves both the quality and duration of analgesia. Since 1979,Morphine is used as an adjunct to spinal anaesthesia for postoperative pain(2).Morphine primarily acts on mu and kappa opioid receptors . Activation of opioid receptors results in inhibition of the presynaptic release and postsynaptic response to excitatory neurotransmitters (e.g. acetylcholine, substance P) from nociceptive neurons. Clinical effects of intrathecal morphine are spinal analgesia (kappa receptor) and supraspinal analgesia (mu1 receptor). Unwanted side effects are respiratory depression, muscle rigidity, and sedation but with doses less that 300mcg these side-effects were minimal(3). Intrathecal morphine, in low doses, in combination with spinal anaesthesia has been safety used in caesarean sections, TURP, gynaecological and orthopaedic surgeries.

Clonidine is an alpha-2 agonist. Clonidine exerts its action on the sensory nerves in the spinal cord by depressing C-fibre neurotransmitters and hyperpolarization of post synaptic dorsal horn neurons. Clonidine's ability to prolong motor paralysis is due to its affinity for alpha-2 postsynaptic receptors within the dorsal horn. Clonidine has been used in a varying doses ranging from 30 to 300 mcg intrathecally. When given with local anaesthetics the maximum dose used is between 1-2 mcg/kg. Higher does are found to cause unwanted effects such as bradycardia, hypotension, and marked sedation**(4)**. Plateau effect of clonidine is seen around 150 mcg**(5)**. The addition of clonidine has been found to decrease postoperative pain in patients who undergo transurethral resection of prostate(TURP)**(6)**. There has been no known publication on its use in urethroplasty.

AIMS AND OBJECTIVES

Aims:

The aim of the study is to evaluate the effect of intrathecal clonidine versus intrathecal morphine in postoperative pain relief among patients undergoing urethroplasty

Objectives:

1) To compare the effectiveness of intrathecal morphine and intrathecal clonidine to provide postoperative analgesia in patients undergoing urethroplasty surgery.

2) To compare the effect of intrathecal morphine and intrathecal clonidine on postoperative sedation, postoperative nausea and vomiting and time to mobilization.

Hypothesis:

Intrathecal clonidine is as effective as intrathecal morphine in treating postoperative pain in patients undergoing urethroplasty surgery with less unwanted effects of morphine.

REVIEW OF LITERATURE

PAIN:

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.(7)

MECHANISM OF PAIN:

Pain has been classified as acute pain which is physiological and does not last for more than 3 to 6 months duration and chronic pain ,that is pathological which is lasting for more than 3-6 months, or persisting beyond the time for tissue healing.(8) It can be produced due to mechanical, chemical, or thermal stimuli. Pain sensation has an afferent and efferent pathway. Pain sensation arises from the unmyelinated dendrites of sensory neurons located around the hair follicles and in deep tissues. Nociceptor impulses are transmitted via Aδ fibers (myelinated) and C fibres (unmyelinated). The noxious stimuli produce electrophysiological activity in nociceptive primary afferent nerve fibres due to the release of mediators released by damaged cells. This results in transport of chemicals such as neurotrophins along axons to the cell bodies of the dorsal root ganglia, which results in alteration of the chemistry and physiology of the sensory cell. Modulation of sensory impulses occurs both at the dorsal horn of the spinal cord and also by descending control systems originating in the cortex, thalamus and brainstem. Transmission of sensory impulses occurs to various parts of the central nervous system which results in registration and localization and production of affective responses. Brain doesn't have a

discrete pain centre. The responses to pain are produced through integrated activity of various areas of the brain.

The somatosensory pathways involved in the transmission of pain are spinothalamic tract and spinoreticular pathway. The fibres from the nociceptors synapse on neurons in the dorsal horn. The axon of these neurons cross the mid line and forms the spinothalamic tract which synapses in the VPL nuclei. The painful input received by the other dorsal horn neurons synapses in the reticular formation of the brain stem and forms spinoreticular pathway and then project to the contralateral thalamic nucleus.

Pain processing includes four elements(9)-

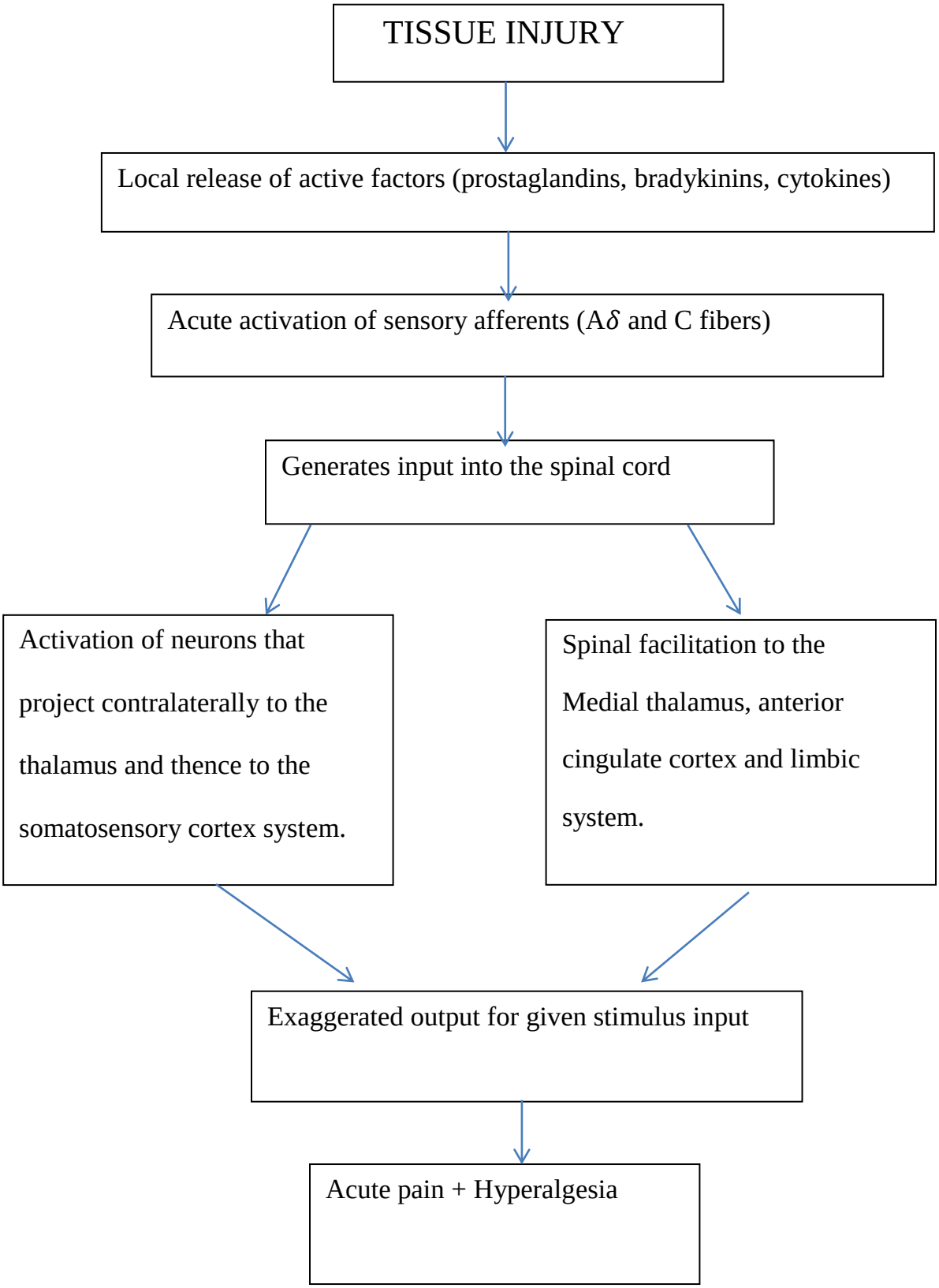
1) Transduction: It is a process of conversion of noxious stimuli into an action potential

2) Transmission : It is conduction of action potential through the nervous system via the first-, second-, and third-order neurons ,which have cell bodies located in the dorsal root ganglion, dorsal horn, and thalamus.

3) Modulation: It involves either inhibition or augmentation of the pain signals and perception by altering afferent neural transmission along the pain pathway.

4) Perception: It is the final common pathway, which is due to integration of painful input into the somatosensory and limbic cortices. Our traditional anaesthetic technique target or treat only this component of pain processing.

Schematic representation of acute pain pathway:



CLINICAL IMPLICATIONS OF PAIN:

There are many systemic side effects due to poorly managed pain. The cardiovascular side effect consists of increase in heart rate, blood pressure and cardiac workload. Intraoperative blood loss will be more due to rise in blood pressure. The respiratory system is also affected. There may be splinting of the respiratory muscle due to pain which results in decrease in vital capacity and atelectasis. Poor respiratory effort in the postoperative period results in retained secretions in the alveoli which becomes a source of infection. There is an increased chance of urinary retention but this may not be a problem for urethroplasty patients as they all have indwelling urinary catheter. Pain prevents early postoperative mobilization which increases the risk for thromboembolism. Pain creates anxiety and fear which finally results in poor patient satisfaction.

ASSESSMENT OF PAIN:

Assessment of pain is essential for effective pain management. For assessment of pain intensity in the postoperative period, the well-known visual analogue scale (VAS) and numeric rating scale (NRS) are equally sensitive and they are both superior to a four-point verbal categorical rating scale (VRS).(10) They are more useful for the assessment of the patient's subjective feeling of pain intensity. They may be used for pain assessment over the last 24 h, or during the last week. The numerical rating scale (NRS) consists of numbers from 0 to 10. 0 equates to no pain and a score of 10 is worst pain imaginable. Assessment of the intensity of pain when the patient is mobile and taking deep breathing, and coughing is as important as assessing pain at rest after surgery because inadequate

dynamic pain relief increases risks of cardiopulmonary complications and thromboembolic phenomenon after surgery. Immobilization in the postoperative period may result in chronic hyperalgesic pain.

MANAGEMENT OF ACUTE POST-OPERATIVE PAIN:

As per ASA guidelines, the management of perioperative pain should include appropriate dose adjustments of medications to avoid abstinence syndrome, to treat pre-existing pain and preoperative initiation of therapy for postoperative pain management.(11) Patient and family education is important in achieving comfort, reporting pain, and in proper use of the recommended analgesic methods. Administration of two or more drugs that act by different mechanisms, i.e., multimodal techniques is proven to be more effective in providing analgesia in the postoperative period. They can be given by any route of administration. The various modalities of pain management in postoperative urethroplasty patients are

- Oral or intravenous acetaminophen ,Non-steroidal anti-inflammatory drugs (NSAIDs) and Cyclooxygenase inhibitors(COX-2 inhibitors)
- Opioids, i.e., oral or intravenous tramadol, subcutaneous morphine, PCA (patient controlled analgesia) morphine, Fentanyl or buprenorphine patch.
- Central Neuraxial techniques include injection of drugs into the epidural and subarachnoid space. It may be either single injection of opioids or non-opioids drugs like clonidine ($\propto 2$ agonist) with or without local anaesthetics intrathecally

or in to the epidural space or continuous epidural infusion of local anaesthetics with or without adding opioids.

Each of the above mentioned modalities have their own advantages and disadvantages. NSAIDs are inhibitors of cyclooxygenase which prevents formation of Prostaglandin E2 from arachidonic acid. NSAIDs provide excellent analgesia but may contribute to postoperative nausea and vomiting. In addition they may also result in platelet dysfunction, which may worsen or precipitate haemorrhage. The concerns regarding COX-2 inhibitors are that they may cause adverse cardiovascular effects.

Opioid analgesics are commonly used drugs for the treatment of postoperative pain. They exert their analgesic effects through μ receptors in the CNS by directly modulating the nociceptive process. They can be administered in different routes such as subcutaneous, intramuscular, intravenous or by central Neuraxial techniques. After major surgeries opioid analgesics are commonly given through Patient-controlled analgesia (PCA). A variety of narcotic medications like morphine, hydromorphone, meperidine, fentanyl can be self-administered using this programmable delivery system (12). The incidence of opioid-related side effects resulting from using intravenous PCA is similar to other routes of administration(13). The prolonged analgesic efficacy of opioids is limited by the development of tolerance. The other side effects of opioids are nausea, vomiting, sedation, respiratory depression through depression of brainstem control of respiratory drive, decrease in blood pressure which is common in hypovolemic patients and urinary retention. Morphine administration results in histamine release and may produce flushing,

tachycardia, hypotension, pruritus, and bronchospasm. Prolonged administration of morphine slows down gastrointestinal transit time and results in constipation and ileus in many patients.

Continuous epidural infusion is one of the commonly practiced methods for pain management both intra-operatively and postoperatively in patients undergoing major abdominal and perianal surgeries. Either low concentration of local anaesthetics or combined with opioids are used as infusions. It provides good analgesia in majority of patients when infusion is given at appropriate dermatome level.(14) Correct placement of epidural catheter requires technical expertise. The most common reason for poor pain control in patients with epidural infusion is malposition or dislodgment of epidural catheter. Other serious but less common complications are profound hypotension, migration of the epidural catheter into intravenous or subarachnoid space, epidural abscess formation, and epidural hematoma which may result in serious neurological sequaelae.

URETHRAL STRICTURE:

Urethral stricture is narrowing of urethra caused due to inflammation or due to scar tissue after trauma like pelvic fractures, urinary catheterization, prostate surgeries or post radiation. It is more common in male population(15). It is almost always acquired condition and mostly iatrogenic. (16)

Common symptoms include urinary retention, strong urge to urinate and frequent urination, painful or difficulty in urinating, slow urine stream, swelling of the penis, loss of bladder control, pain in the lower abdomen and pelvic region, blood in the semen, discharge from the urethra, bloody or dark urine

ANATOMY OF MALE URETHRA:

Normal male urethra is a fibro muscular tubular structure, 18-20 cms long. It starts at the internal urethral orifice in the trigon of the bladder and opens in the navicular fossa of the glans penis at the external urethral meatus, which is the narrowest part of the urethra. It is divided in to a posterior part and an anterior part. The posterior part, which extends from the bladder neck to the distal external urethral sphincter, can be divided into the prostatic and the membranous urethra. Membranous urethra is 1 cm long and it passes through the urogenital diaphragm, surrounded by sphincter urethrae. It is the shortest and narrowest portion of urethra. Prostatic urethra is 3 cm long and is surrounded by the prostate gland. On its posterior wall lies the smooth muscle verumontanum which receives the ejaculatory ducts.

The anterior urethra extends from the distal external urethral sphincter to the external urinary meatus and is divided into the bulbar, penile and navicularis urethra(17). Penile or spongy urethra is16 cm long and is encased by corpus spongiosum of the penis. It is the longest portion of male urethra. Bulbar or bulbous urethra traverses the root of the penis and it receives the ducts from the bulbourethral glands and the glands of Littre . Patients with urethral strictures complains of voiding symptoms like slow stream,

intermittent stream, straining, hesitancy, increased daytime frequency, urgency, nocturia ,acute urinary recurrent urinary tract infection(18).Various surgical interventions for urethral stricture are urethrotomy (optical cold knife urethrotomy) , simple urethral dilatation and urethroplasty (anastomotic or substitution).The type of surgical intervention required depends on length of the stricture: less than 2 cm versus more than 2 cm, location of the stricture, bulbar versus penile, number of previous interventions: two or more versus less than two(19).There is an increased trend towards urethroplasty as primary intervention are associated with recurrence and eventual urethroplasty(20).

Nerve supply of male genitalia:

Male genitalia are supplied by the pudendal nerve (S2-S4). The perineal branch of the pudendal nerve supplies the posterior part of the scrotum and the rectal nerve to the inferior rectal area. Cutaneous innervation of penis and scrotum arises from the dorsal and posterior branch of the pudendal nerve. The ilioinguinal nerve supplies the anterior part of the scrotum and proximal penis after it exits the superficial inguinal canal. The ischiocavernous and bulbocavernous muscles are supplied by the pudendal nerve. The pudendal nerve branches into the inferior rectal nerve and the scrotal nerve and continues as the dorsal nerve of the penis.

Autonomic nerves supply is from sympathetics that arise from lumbar segments L1 and L2 and parasympathetics from S2-4 (Nervi erigentes or pelvic nerve). Lumbar splanchnic nerves join the superior hypogastric plexus over the aortic bifurcation, left common vein and sacral promontory. From this plexus, right and left hypogastric nerves travel medial

to the internal iliac artery to the inferior hypogastric plexus. The pelvic plexus adjacent to the base of the bladder, prostate, seminal vesicles and rectum contain parasympathetic fibres as well. Nerves from the inferior pelvic plexus supply the prostate, seminal vesicles, epididymis, membranous and penile urethra and bulbourethral gland.

The cavernous nerves arise from the pelvic plexus. They supply the corpus cavernosum and penile urethra, and terminate in a delicate network around the erectile tissue.

URETHROPLASTY:

Urethroplasty is the repair of an injury or defect within the walls of the urethra.

Types of urethroplasty:

The different types of urethroplasty surgeries are anastomotic, buccal mucosal on lay graft, scrotal or penile island flap (graft), and Johansen's urethroplasty.(21) The choice of procedure depends on many factors like:

- length of the defect
- physical condition of the patient
- availability of auto graft tissue(buccal mucosa or tissue from penis or scrotum)
- multiple or single stricture

Preoperative evaluation:

This consists of identification of medical co-morbidities and optimization of the same. Investigations include routine blood investigations, urine analysis and urine culture and

investigations for the underlying comorbid illness and specifically for the urethral stricture assessment like Post void residual urine, Uroflometry, Micturiting Cysto-urethrogram, Urethroscopy, Cystoscopy and ultrasonography of the abdomen and pelvis.

Positioning for surgery:

The frequently used position during urethroplasty is lithotomy with a trendelenburg tilt (head down tilt). Lithotomy position include – 80 to 100 degree of flexion at hips, 30 to 40 degree abduction from the midline and flexion of knee such that the leg may lie parallel to the trunk. The legs are held up with the help of stirrups. The lower extremities are padded to prevent compression against the stirrups. For placing the patient in lithotomy position, coordinated positioning of the lower extremities of patient by two assistants is essential to avoid torsion of the lumbar spine. The foot section of the surgical table is lowered and head-down tilt (trendelenburg position) will be given.

Pathophysiological changes during lithotomy and trendelenburg position(22)**:**

Cardiovascular effects:

When the legs are elevated and head is lowered venous return increases and results in transient increase in cardiac output. This reduces perfusion gradients to the lower limbs and improves access to the perineal surgical site.

Respiratory effects:

Lithotomy position results in cephalad displacement of diaphragm by the abdominal viscera resulting in reduction of lung compliance which subsequently results in decrease in tidal volume. Head down tilt results in increased venous return from lower extremities. This causes reflex vasodilation and congestion of poorly ventilated lung apices and results in ventilation and perfusion mismatch.

Neurological effects:

The common peroneal nerve is the most commonly involved nerve in positioning related neuropathy It comprises 78% of nerve injuries in lithotomy position.

Compartment syndrome:(23)

In lithotomy position compression of calf muscles results in venous stasis and venous thromboembolism and compartment syndrome. It is more common in prolonged surgeries (surgeries >5hrs duration).

Early clinical manifestations of compartment syndrome(24) include pain in the affected extremity, oedema, pain on external pressure. Late clinical signs include absence of distal pulses, paraesthesia and paresis. Symptoms and signs are generally not reliable for the diagnosis. Postoperatively, difficulties with pain control might be the only sign. Differential diagnosis includes DVT, arterial injury and peripheral nerve damage.

Surgical technique:

Anastomotic urethroplasty:

- Patient positioned in lithotomy position and local preparation done.
- Methylene blue is injected into the urethra.
- The distal extent of the stenosis is identified by inserting a 16- French catheter with a soft round tip.
- Midline perineal incision is made.
- The urethra is freed from the bulbocavernous muscle.
- The urethra is dissected from the corpora cavernosa.
- The distal extent of the stenosis is identified and outlined.
- The urethra is transected at the stricture level.
- The stricture is resected and the urethra is spatuled for 1 cm on both ends. A total of 10 interrupted 4-zero polyglactin sutures are put in place before tying.
- A Foley 16-French grooved silicone catheter is inserted and the urethra is closed and the anastomosis is completed on the roof.
- Once the anastomosis is completed two ml of fibrin glue are injected over the urethra to prevent urinary leakage.

Substitution urethroplasty:

- Two surgical teams work simultaneously.
- The steps are similar to anastomotic urethroplasty till the dissection of urethra from the corpora cavernosa and identification and outlining the distal extent of the stenosis.
- The urethra is transected at the stricture level and the distal and proximal urethral ends are mobilized from the corpora cavernosa.
- The distal and proximal urethral ends are fully spatuled along the dorsal surface.
- Two ml of fibrin glue are injected over the urethra and the buccal mucosal graft is applied over the fibrin glue.
- The distal and proximal urethral edges are sutured to the apices of the graft. The distal urethra is pulled down and the proximal urethra is pulled up to cover the graft.
- The distal and proximal urethral edges are sutured together along the midline as an end-to-end anastomosis.

Post-operative care:

The average duration of post procedure hospital admission is approximately 3 days. Patient is maintained on oral antibiotics until the catheter is removed. Two weeks following surgery, the catheter is removed and voiding cysto-urethrography is obtained

Complications of urethroplasty:

Early complications:

- Wound dehiscence
- Scrotal hematoma
- Erectile dysfunction
- Catheter dislodgement
- Wound infection

Late complications:

- Erectile dysfunction
- Post void dribbling
- Diverticulum
- Fistula
- Chordae
- Recurrence

HISTORY OF NEURAXIAL ANAESTHESIA:

Bier made history by using cocaine for intrathecal anaesthesia in 1898(25).Later on Neuraxial anaesthesia was successfully performed using different local anaesthetics like procaine by Braun (1905), tetracaine by Sise (1935), lidocaine by Gordh (1949), chloroprocaine by Foldes and McNall (1952), mepivacaine by Dhunérand Sternberg

(1961), and bupivacaine by Emblem (1966)(22). In the 1980s spinal anaesthesia using ropivacaine and levobupivacaine was introduced.

Despite the vast experience in neuraxial techniques through the past century, several adverse events like paraplegia after spinal anaesthesia (Woolley and Roe in 1954), persistent neurologic deficits, adhesive arachnoiditis with spinal chloroprocaine , and cauda equina syndrome with continuous spinal lidocaine anaesthesia were reported. Recently, the potential for catastrophic epidural hematoma with newer potent anticoagulants (e.g., low-molecular-weight heparin [LMWH]) and antiplatelet agents (e.g., clopidogrel) has caused concern.

ANATOMY OF SPINAL CORD:

The spinal cord extends from brainstem proximally and terminates distally in the conus medullaris as the filum terminale and the cauda equina. In infants it ends at L3 vertebral body and in adults at the lower border of L1. Inside the bony vertebral column, spinal cord is surrounded by three membranes, the pia mater, the arachnoid mater, and the dura mater from within to outside. The cerebrospinal fluid (CSF) is present in the space between the pia mater and the arachnoid mater which is termed as subarachnoid or intrathecal space. The arachnoid mater is a non-vascular membrane which acts as the principal barrier to drugs crossing into and out of the CSF. The epidural space surrounds the duramater and extends from the foramen magnum to the sacral hiatus. It is bounded anteriorly by the posterior longitudinal ligaments, laterally by the pedicles and intervertebral foramina, and posteriorly by the ligamentum flavum. The epidural space

contains nerve roots, fat, areolar tissue, lymphatics, and blood vessels including the Batson venous plexus. Posterior to the ligamentum flavum is the lamina and spinous processes of vertebral bodies or the interspinous ligaments. Extending from the external occipital protuberance to the coccyx posterior to these structures is the supraspinous ligament, which joins the vertebral spines.

SPINAL ANAESTHESIA:

Subarachnoid block is an anaesthetic technique where anaesthesia is provided by injecting local anaesthetic in to the subarachnoid space. It is mainly used for lower abdominal surgeries, surgeries in the perineal region and lower limb surgeries.

Technique of spinal anaesthesia:

For giving spinal anaesthesia, patient is positioned in sitting or lateral decubitus position. Once skin preparation is done with antiseptic solution like betadine or chlorhexidine and the patient is draped. A 25G Whitacere or 25G Quinkes spinal needle is usually used in our institution to enter and administer drug into the subarachnoid space. Skin is infiltrated with 2% lignocaine prior to introducing spinal needle. Subarachnoid space is reached by either median or para-median approach. In median approach the palpating fingers are rolled from side to side and cephalad to caudad to identify the interspinous space. The highest point of iliac crest is used as landmark. The line joining the two iliac crests crosses the body of L4 or corresponds to L4-L5 intervertebral space. In para-median approach spinal needle is inserted 1 cm lateral and 1 cm caudad to the caudad edge of the

more superior vertebral spinous process and approximately 15 degrees off the sagittal plane. Spinal needle has to pass through skin, subcutaneous fascia, supraspinous ligament, interspinous ligament, ligamentum flavum and dura to reach the subarachnoid space. On passing through the dura there is a sensation of loss of resistence or pop sensation. Subarachnoid space is confirmed by free flow of C.S.F after removing stylet from the needle.

Mechanism of action:

For spinal and epidural anaesthesia, the target binding sites are located within the spinal cord (superficial and deep portions) and on the spinal nerve roots in the subarachnoid and epidural spaces. The spinal nerve roots and dorsal root ganglia are considered the most important sites of action. Diffusion is the primary mechanism of local anaesthetic distribution in the CSF from areas of high concentration toward other segments of the spinal cord with low drug concentration. Rostral spread after the administration of a small local anaesthetic dose, often evident within 10 to 20 minutes, is related to the CSF circulation time. Longitudinal oscillations generated by the pulsations of the arteries in the skull are believed to be responsible for CSF bulk flow. This likely facilitates the cephalad distribution of drug from the lumbar intrathecal space to the basal cisterns within 1hour of injection.

BUPIVACAINE:

Bupivacaine was introduced in 1963 and it was used successfully for spinal anaesthesia by Emblem in1966(22). It is a highly protein-bound amide local anaesthetic with a slow onset because of its relatively high pKa. It is appropriate for procedures lasting up to 2.5 to 3 hours. For central neuraxial blocks 0.5% preservative free bupivacaine is used.

Mechanism of action:

It binds to the sodium channels on the nerve fibres and inhibits the passage of sodium ions through ion selective sodium channels in nerve membranes and there by slows down the rate of depolarization of nerve action potential such that the threshold potential is not reached. It results in inhibition of transmission of nerve impulses. ATP- sensitive potassium channels in the cardiac muscle fibres are also sensitive to bupivacaine which explains the reason for cardio toxicity in cases which exceed the toxic doses.

MORPHINE:

Morphine is a hydrophilic phenanthrene derivative. It is approximately 100 times less potent than fentanyl. When compared to the lipophilic opioids, it has slow onset of action (15 minutes intrathecal, 30 minutes epidural), and significantly longer duration of action (approximately 12-24 hours). Its terminal elimination half- life is approximately 170 minutes. It produces analgesia, sedation, euphoria etc. Analgesia is prominent when it is given before painful stimulus occurs.

NEURAXIAL OPIOIDS: (25)

The first published report on opioids for intrathecal anaesthesia belongs to a Romanian surgeon, Racoviceanu-Pitesti, who presented his experience at Paris in 1901(26). Behar and his colleagues published the first report on the epidural use of morphine for the treatment of pain in The Lancet in 1979.(26)

Mechanism of action:

Opioids act as agonists at opioid receptors that are located in different body tissues including the brain (cerebral cortex, thalamus, hypothalamus, amygdala, basal ganglia, brainstem, reticular activating system), spinal cord and non-neural tissues such as the gastrointestinal tract. Opioid receptors are classified in to four main groups- mu, kappa, delta and nociceptin. They belong to G-protein coupled inhibitory receptors. Different opioids have different affinities for these receptors and each class is associated with specific therapeutic and adverse effects. Neuraxial opioid administration provides analgesia by primarily binding to pre and postsynaptic mu-opioid receptors in the substantia gelatinosa of the dorsal horn of the spinal cord. There is decreased conductance through voltage gated calcium channels and reduced calcium influx with subsequent decreased neurotransmitter release with activation of presynaptic receptors on primary afferent neurons carrying nociceptive information. It results in reduction of signalling between primary and secondary afferent neurons in the dorsal horn. Opioid binds to the postsynaptic opioid receptors on secondary afferent neurons which results in hyperpolarisation and decreased propagation of action

potentials. Intrathecal opioids act as ligands on opioid receptors in three different areas and produce analgesia:

1. Their main site of action is dorsal horn of the spinal cord.

2. They modulate descending inhibitory pain pathways when they are transported supra-spinally by bulk CSF flow .

3. Minor analgesic effect is due to the diffusion of small amount of opioid into the epidural space and subsequent systemic absorption which results in centrally mediated analgesia.

Intrathecal opioids undergo minimal metabolism within the CSF. Lipid solubility of the opioid determines the onset and duration of analgesia and the degree of cephalad spread. Highly fat soluble opioids like fentanyl and sufentanil rapidly diffuse into the spinal cord and binds to the dorsal horn receptors. This produces a rapid onset of analgesia with less cephalad spread and low risk for delayed respiratory depression, but the duration of analgesia is relatively short. Morphine is water soluble, so it binds slowly to the dorsal horn receptors and results in a slower onset but more prolonged duration of analgesia. There is increased cephalad spread and subsequently an increased risk of delayed respiratory depression. The effects of opioids within the CSF are complex, because of a combination of direct spinal cord dorsal horn opioid receptor activation, cerebral opioid receptor activation after CSF transport, and peripheral and central systemic effects after vascular uptake. The effect at each of these sites depends on both

the dose administered and the physicochemical properties of the opioid, particularly lipid solubility. The spread of lipophilic opioids within the CSF is therefore more limited than hydrophilic opioids such as morphine, which demonstrate greater spread as a result of slower uptake and elimination from the CSF.

Most common side effects of neuraxial opioids include:

- Pruritus
- Nausea and Vomiting
- Ventilatory depression
- Sedation
- Urinary retention

Pruritus:

It is one of the most common side effects with injection of opioids in to the epidural or subarachnoid space. It is a subjective and unpleasant sensation which provokes patient to scratch and is more localized to the face, neck, or upper thorax. It is usually localised to face supplied by the trigeminal nerve. The mechanism is likely due to the cephalad migration of the drug which interacts with opioid receptors in the trigeminal nucleus. This nucleus is rich in opioid receptors and is continuous with the substantia gelatinosa and Lissauer tract at C3-C4. Naloxone, an opioid antagonist is effective in relieving opioid induced pruritus.

Ventilatory Depression:

The incidence of ventilatory depression after giving neuraxial opioids requiring treatment is 1percent(27). It may occur within 2hrs of neuraxial injection of opioid and may be due to systemic absorption. Delayed ventilatory depression occurs 6 to 12 hours after neuraxial injection of the drug. It is usually attributed to the cephalad migration of drug in the CSF and interaction of the drug with opioid receptors located in the ventral medulla. The risk factors for opioid induced ventilatory depression include increasing age, use of long-acting sedatives along with opioids, positive pressure ventilation, and pre-existing respiratory disease. When opioid analgesics are used during the first 12–24 h after intrathecal administration of morphine it results in development of early and late onset respiratory depression.

Nausea and Vomiting:

It is due to direct stimulation of the dopaminergic receptors of chemoreceptor zone (CTZ) in the floor of fourth ventricle. The chemoreceptor zone contains several different receptors that modulate its activity. It lies outside the blood–brain barrier. Most of the medications used to treat PONV act by either a direct or indirect antagonizing action of emetogenic substances on receptors in the CTZ. The known risk factors include female gender from puberty, non-smoking status, previous history of PONV or motion sickness, and genetic predisposition, use of inhalation agents, nitrous oxide, large-dose neostigmine, and intraoperative and postoperative opioid use, longer duration of surgery.

Multimodal therapy is more effective in preventing and treating PONV. They include serotonin antagonists like ondansetron, neurokinin, antihistamines, and benzodiazepines.

Sedation:

It is dose dependant. Doses up to 500 micrograms were used without significant side effects.(28)

Dose of intrathecal morphine:

There are many studies done in the past using different doses of intrathecal morphine ranging from 100 µgms to 4000 µgms for various surgeries. In the meta-analysis done by Meylan et al it was concluded that the unwanted side-effects were more in intrathecal morphine group who received more than 300 µgms(29).

CLONIDINE:

Clonidine is an imidazole which is a centrally acting selective partial alpha-2 adrenergic agonist and partial alpha adrenergic antagonist. It was first synthesized in 1962 as nasal decongestant, and marketed as antihypertensive in 1972. It has high affinity for these receptors and relatively low affinity at these sites. It decreases sympathetic nervous system output from the central nervous system.(30)

Mechanism of action:

Clonidine acts as an alpha-agonist in the anterior hypothalamus and excites a pathway that inhibits excitatory cardiovascular neurons. It acts on the nucleus tractus solitarus

(NTS) and results in increased inhibition of sympathetic outflow from the vasomotor centre. In the posterior hypothalamus , it acts as an alpha-antagonist and decreases excitation of excitatory cardiovascular neurons, or it decrease norepinephrine release by acting as an alpha-presynaptic agonist and thus decreases excitation of excitatory cardiovascular neurons.(30) In the medulla it acts as an alpha-antagonist, inhibits excitatory input to the sympathetic nervous system and enhances the excitatory vagal cardiac reflex and the inhibitory baroreceptor reflex. All of these actions produce diminished sympathetic outflow from the CNS, which results in decreased arterial blood pressure.

It acts on pre-junctional and post-junctional α2 receptors in the dorsal horn of the spinal cord. Activation of presynaptic receptors reduces neurotransmitter release, whereas post-junctional receptor activation results in hyperpolarization and reduction of pulse transmission.

Alpha 2 consists of three subtypes. Alpha 2A, 2B, 2C. Clonidine acts on Alpha2A receptors and results in sedation, analgesia and sympatholysis.

Most common side effects of clonidine are:

- Bradycardia
- Hypotension
- Sedation
- Xerostomia

Bradycardia:

Tachycardia is attenuated through block of the cardio-accelerator nerves. Bradycardia is due to vagal stimulation. Treatment of symptomatic bradycardia is Intravenous anticholinergic.

Hypotension:

Clonidine acts on Alpha 2 adrenergic receptors of peripheral blood vessels and results in vasodilation. The decrease in systolic blood pressure is more prominent than the decrease in diastolic blood pressure.

Sedation:

Clonidine acts on locus cerulus of brain stem and results in sedation. Assessment of sedation is important as it may result in respiratory depression which is potentially disastrous. There are many scoring systems available to assess the degree of sedation like Richmond Agitation-Sedation Scale (RASS), Ramsay Sedation Scale (31), Pasero Opioid-induced Sedation Scale (POSS)(32).

Dose of intrathecal clonidine:

The dose of intrathecal clonidine is 75-150µgms. In the randomised control trails done by Tuijl et al and Ranju singh et al in caesarean section patients using 75 µgms intrathecal clonidine does not increase the incidence of side-effects(41) (42). Sethi B. et al used 1 µgm/kg body weight clonidine for intrathecal injection in patients undergoing lower

abdominal surgeries which concluded that it increases duration of post-operative analgesia with increased sedation and decrease in heart rate and blood pressure which does not require any therapeutic intervention (37). A clinical review showed that doses more than 75 µgms resulted in significant hemodynamic changes (43).

PATIENT SELECTION AND METHODOLOGY

Settings:

This study was carried out in the urology operating theatres and urology ward of Christian Medical College and Hospital, Vellore. The Department of urology performs about 150-200 urethroplasty surgeries per year.

Inclusion Criteria:

- Age between 18 to 65 years
- ASA – 1 & 2
- Informed consent obtained

Exclusion Criteria:

- Refused consent
- Cardiac arrhythmias
- Alpha adrenergic receptor blocker medication, Calcium channel blocker medication, ACE inhibitor medication and β-blockers.
- Psychiatric illness
- Known allergies to either: local anaesthetics, opioids and alpha-2 agents
- Contraindications for spinal anaesthesia
- Bodyweight>80kgs

METHODOLOGY:

Type of study:

Prospective Randomized Controlled double blinded study where the patient and principal investigator were blinded.

Method of randomization:

Permuted block randomization of size 2, 4 or 6 of varied proportion was generated using SAS 9.1.3 computer software.

Method of allocation concealment:

Serially numbered opaque sealed envelopes with the random sequence were generated and one envelope was opened in the operation theatre just prior to taking up the patient for surgery and the treatment allocation was provided according to the sequence mentioned in the envelop.

Blinding and masking:

Double blinding where Principal investigator and the subject were blinded.

Primary Outcome:

Postoperative analgesia:

It was assessed using VAS score. It consists of a horizontal line that measures 10 cms in length. It is tagged at each end with a word descriptor (0-no pain, 10-worst pain ever

had). The patient was shown this scale and asked to mark the point that represents their current pain status. This is used to assess pain over 24 hours at different time intervals. Its greatest advantage is that it is simple to use (10).

Secondary Outcomes:

• Postoperative sedation:

It is assessed using Ramsay sedation score. It is graded from 1to 6 depending the depth of sedation

1. Anxious or restless or both
2. Cooperative, orientated and tranquil
3. Responding to commands
4. Brisk response to stimulus
5. Sluggish response to stimulus
6. No response to stimulus

• PONV (postoperative nausea and vomiting):

It is assessed using PONV scoring system which has scores from 0 to 3 depending on the severity of nausea and vomiting.

0- No nausea and not vomiting

1- Light nausea or vomiting without previous nausea

2- 2-Moderate nausea and/or vomiting

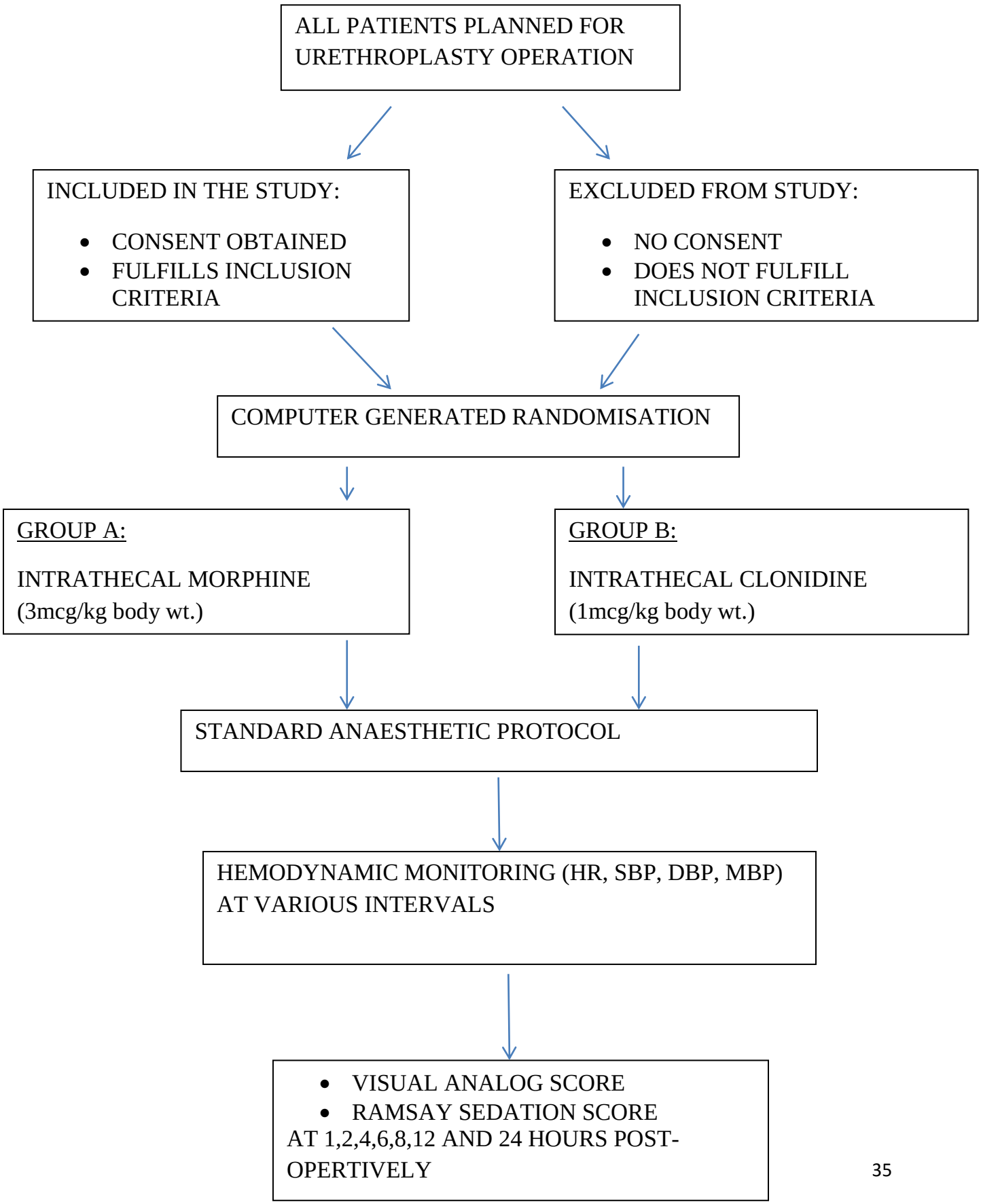
3- 3- Severe nausea and/or reoccurring vomiting

• **Time to mobilization**

JUSTIFICATION FOR STUDY:

Central neuraxial opioids have the advantage of selective analgesia without sensory or motor blockade. But the potentially catastrophic side effects such as delayed respiratory depression have prompted further research to develop non opioid analgesics with less side effects. Intrathecal clonidine is extensively used in various studies as an alternative to neuraxial opioids for control of pain. It is proven to be a potent analgesic agent with less opioid related side effects (6). It is given intrathecally in labour analgesia and orthopaedic surgery as a sole analgesic agent or mixed with opioids and local anaesthetics. However there is still dearth of studies using intrathecal clonidine for postoperative analgesia in urethroplasty surgeries

Detailed diagrammatic Algorithm of the study:



The study was approved by the institutional review board, and the participants who fulfil the inclusion criteria were enrolled for the study after taking informed consent. Information sheet and consent form were provided in the preoperative period. Consent was obtained after explanation by the primary investigator the day before surgery and video recording of consent process was done. No premedication was given on the day of surgery. In the operating room intravenous access was obtained and standard monitoring such as E.C.G, pulseoximeter, non-invasive blood pressure monitoring was done to all patients. The patients were randomly allocated into two groups using a computer generated block randomization. Group A received intrathecal morphine and Group B received intrathecal clonidine.

Under strict aseptic conditions, using 25 gauze Whitacere needle, intrathecal space confirmed by free flow of C.S.F, preservative free clonidine (1microgram/kg body weight) with a maximum dose of 75 mcg or morphine (3 micrograms/kg body weight) with a maximum dose of 300mcg is mixed with 2ml of 0.5% bupivacaine and was injected into the intrathecal space. After intrathecal injection of study drug general anaesthesia was given using I.V Fentanyl 1-2mcg/kg and I.V Propofol 1-2mg/kg and muscle relaxation achieved with 0.1 mg/kg Vecuronium. Patient was intubated with either appropriate size nasal RAE tube or oral endotracheal tube depending on whether buccal graft is being used for urethral reconstruction. Then patient was mechanically ventilated and maintained on 50% oxygen and Isoflurane. All patients received Inj. Paracetamol 1gm I.V prior to incision. Heart rate, systolic, diastolic blood pressure and

mean arterial blood pressure were recorded before and after intrathecal administration of drug, at the time of incision and in the recovery room. For every increase in heart rate and mean arterial pressure above 20% of baseline was treated with inj. Fentanyl 1mcg/kg up to a maximum of 5mcg/kg. Atropine, 0.3 to 0.6 mg was used to treat clinical relevant bradycardia is defined as <50/min or < 20% of baseline with of

During postoperative period all patients received inj. Ondansetron 8mg I.V q6th hourly. During postoperative period patients were followed for 24hrs and visual analogue score, Ramsey sedation score, nausea and vomiting, time at which patient is mobilized post operatively were recorded at 1, 2, 4, 8, 12 and 24 hours by the primary investigator. Rescue analgesia was given when VAS score greater than 4 which includes inj. Diclofenac 75mg I.V and lignocaine gargles

SAMPLE SIZE:

With expected mean time of 600 (SD=120) minutes and 720(SD=180) minutes in each group the minimum required samples for the study is 24 in each arm (45).

Two Means - Hypothesis testing for two means	
Standard deviation in group I	120
Standard deviation in group II	180
Mean difference	120
Effect size	0.8
Alpha error (%)	5
Power (1- beta) %	78
1 or 2 sided	2
Required sample size per group	24

Statistical Methods:

Data entry was done using Epidata software.

Data analysis was performed using SPSS 16.0 software.

For categorical variables, frequency tables were done and presented as bar plots.

For continuous measurements, which was normally distributed were presented using mean and standard deviation.

Mean:

It is also called the average. It is calculated by dividing the sum of all the data by the number of data.

$X=x1+x2+x3+...../n$

Standard deviation:

This statistical tool tells us how spread out the numbers are, i.e.it shows the range across which our data varies from the mean value. To calculate the standard deviation we need to calculate the mean and variance first.

Non-normal measurements are presented using median and interquartile range (IQR).

Median:

This is the middle value in a set of numbers that has been arranged in ascending order.

Interquartile range (IQR):

It is a measure of variability. The data is divided in to four equal parts and the values that divide each part are called the first, second, and third quartiles. IQR is the difference between the first and third quartile.

Mean comparison between groups using Independent samples t test. (Error plot, histogram).

Pearson chi-squared test:

This is one of the commonly used chi-squared tests. It is used to test a null hypothesis. This is done by two types of comparisons 1) It establishes if a frequency distribution that is there in a study differs from a theoretical distribution 2) It assesses if the paired observation of the two variables studied are independent of each other.

Mann Whitney U test:

For non-normal variables, nonparametric test, Mann Whitney U test is used for group comparison. It assesses if the independent observations made in the two study groups have a higher value than the other.

RESULTS

The data collected have been analysed under the following categories:

1) Pre-operative parameters

2) Intraoperative parameters

3) Post-operative parameters

1) PRE-OPERATIVE PARAMETERS:

The total numbers of patients that was recruited for the study was forty six. Twenty three patients were allotted to each group. Among the patients who were included in the study two patients from the clonidine arm were excluded from analysis, since the urologists after examination under anaesthesia decided not to proceed for urethroplasty surgery.

DESCRIPTIVE STATISTICS:

Table1: This data describes the baseline characteristics of patient.

Variable	Clonidine N=21 Mean(S.D)	Morphine N=23 Mean(S.D)	P value
Age(in years)	39.68±12.63	39.04±9.02	0.846
Height(cms)	165.27±4.92	166.22±6.57	0.589
Weight(kg)	59.77±9.28	64.35±9.56	0.111
BMI	21.94±3.69	23.28±3.19	0.198

Patients between the ages of 18 to 65 years were included in the study. The average age of the participants is the same in both groups. This is a parametric variable, so the statistical test used to analyse this variable is independent sample t-test. The p value is 0.846, suggesting no significant difference in the age of patients included in both the arms of the study. The mean age of male population with urethral stricture was 39 years. Urethral stricture is a condition which is more common in middle aged men.

Evident from the table the mean of heights, weights, BMI were comparable in both groups.

ASA GRADE:

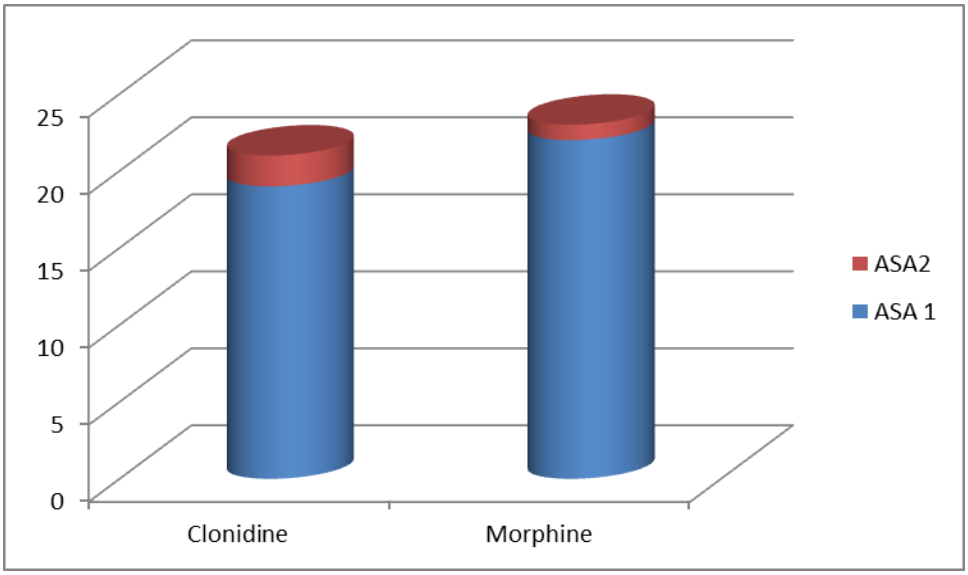
In the six categories physical status classification of American society of Anaesthesiologists (ASA) only grade 1 and 2 patients were included in the study.

Table 2: This table gives the number of patients in each ASA group

Variable	Clonidine n=21(n %)	Morphine n=23(n %)	P value
ASA 1	19(90.47)	22(95.65)	0.608
ASA 2	2(9.52)	1(4.34)	0.608

ASA grade 1= normal healthy individual.

ASA grade 2= patients with mild systemic illness like hypertension and diabetes mellitus which is under control.



Graph 1: Pictorial depiction of number of ASA1 and ASA2 patients in each group

Majority of the patients were ASA grade 1. 90.5% in the clonidine group and 95.7% in the morphine group belonged to ASA grade 1. Patients taking Alpha adrenergic receptor blockers , Calcium channel blockers , ACE inhibitor and ARB medications were excluded from the study to prevent any unwanted side-effects of clonidine like bradycardia and hypotension ,the ASA grade 2 patients included in the study were either patients with diabetes mellitus or hypothyroidism. There was no significant difference between the two arms with regards to the distribution of ASA 1and 2 categories.

It has been studied in the past that certain comorbid illnesses alter pain threshold, pain impulse conduction and the total amount of analgesic requirement. For example, patients who have uncontrolled diabetes mellitus usually have associated neuropathy. Similarly patients with chronic kidney disease may have to be given less amount of opioids. Therefore patients with such comorbidities were not included in the study. (36)

2) INTRAOPERATIVE PARAMETERS:

DURATION OF SURGERY:

This was analysed to know the average surgical time in both groups.

Table 3: This table compares the median time of duration of surgery.

	25^{th} Percentile (in hours)	75^{th}Percentile (in hours)	Median 50thPercentile (in hours) (IQR)
Clonidine,N=21	3.15	5.50	4.0(3.15-5.50)
Morphine,N=23	3.00	5.00	4.00(3.00-5.00)

This parameter was analysed using median as there were skewed or outlying values in both groups. Therefore a mean will not represent the true data. The median duration of surgery was 4hrs. The P value for this data is 0.407.

TIME BETWEEN INJECTION OF DRUG AND PERINEAL INCISION:

This variable is analysed to see whether the surgical stimulus was after the onset of action of the drug.

Table 4: This table shows the mean time between injection of drug and perineal incision.

GROUP	N	Time (minutes)	S. D
Clonidine	21	39.67	21.89
Morphine	23	40.43	22.26

P value: 0.407

The mean duration of time between injection of clonidine and morphine to perineal incision are 39.67±21.89 and 40.43±22.26 minutes.

NUMBER OF PATIENTS FOR WHOM BUCCAL GRAFT IS USED:

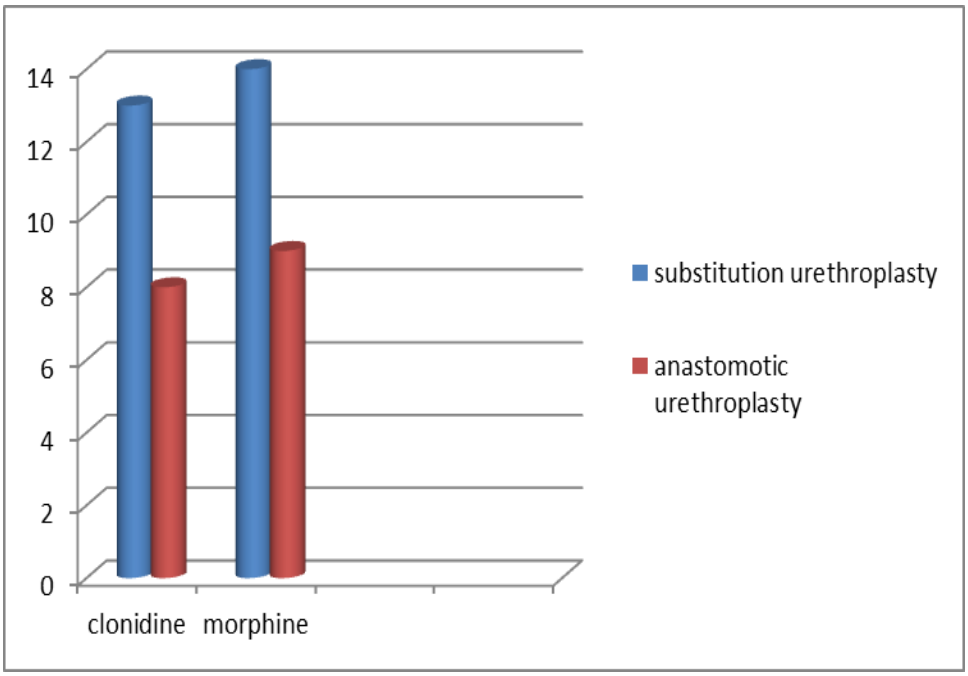
This variable was analysed to know the distribution of patients undergoing substitution urethroplasty in both groups.

Table 5: This table shows the number of patients for whom buccal graft is used.

			GROUP		
			clonidine	Morphine	Total
Type of urethroplasty	Anastomotic	Number of patients	8	9	17
			47.1%	52.9%	100.0%
	Substitution	Number of patients	13	14	27
			48.1%	51.9%	100.0%
Total		Number of patients	21	23	44

This parameter was analysed to know the distribution of patients who underwent substitution urethroplasty in clonidine and morphine group. Out of 44patients 27 patients had undergone substitution urethroplasty for whom buccal graft was used. In the

clonidine and morphine group 48.1% and 51.9% of patients had undergone substitution urethroplasty.



Graph 2: Pictorial depiction of type of urethroplasty in both groups.

HEART RATE AT VARIOUS POINT OF TIME INTRAOPERATIVELY:

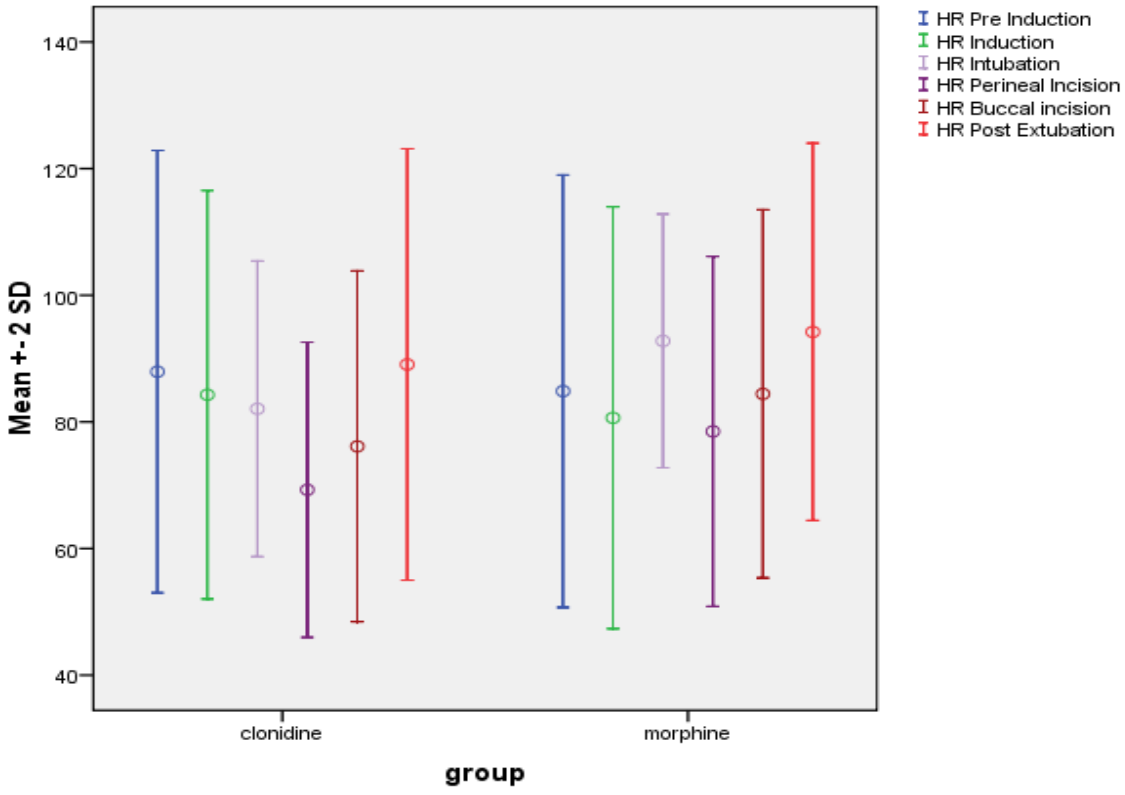
This was analysed to know the response for various stimuli in the intraoperative period.

Table 6: This table shows the mean heart rate with standard deviation at various time intervals.

	GROUP	Mean	S.D	P value
HR Pre Induction	clonidine	87.93	17.464	
	morphine	84.86	17.074	0.449
HR Induction	clonidine	84.29	16.122	0.456
	morphine	80.64	16.658	
HR Intubation	clonidine	82.07	11.672	0.039
	morphine	92.79	10.017	
HR Perineal Incision	clonidine	69.29	11.652	0.216
	morphine	78.50	13.822	
HR Buccal incision	clonidine	76.14	13.856	
	morphine	84.43	14.538	0.135
HR Post Extubation	clonidine	89.07	17.036	0.593
	morphine	94.21	14.895	

The baseline heart rate in clonidine and morphine was 87.9±17.4 beats per minute and 84.86±17.074 beats per minute. As the p value is 0.449 there is no significant difference in the baseline characteristics. The heart rate at intubation in clonidine and morphine

were 82.07±11.672 beats per minute and 92.79 ±10.017 beats per minute which shows significant decrease in intubation response in clonidine group.



Graph 3: Pictorial representation of changes in heart rate at various point of surgery

It was noticed that there is an increase in heart rate in morphine group at the time of intubation while there is a significant obtundation of intubation response in the clonidine group as compared to morphine group as p value is 0.039.

SYSTOLIC, DIASTOLIC BLOOD PRESSURE, MEAN ARTERIAL PRESSURE AT VARIOUS POINT OF TIME INTRAOPERATIVELY:

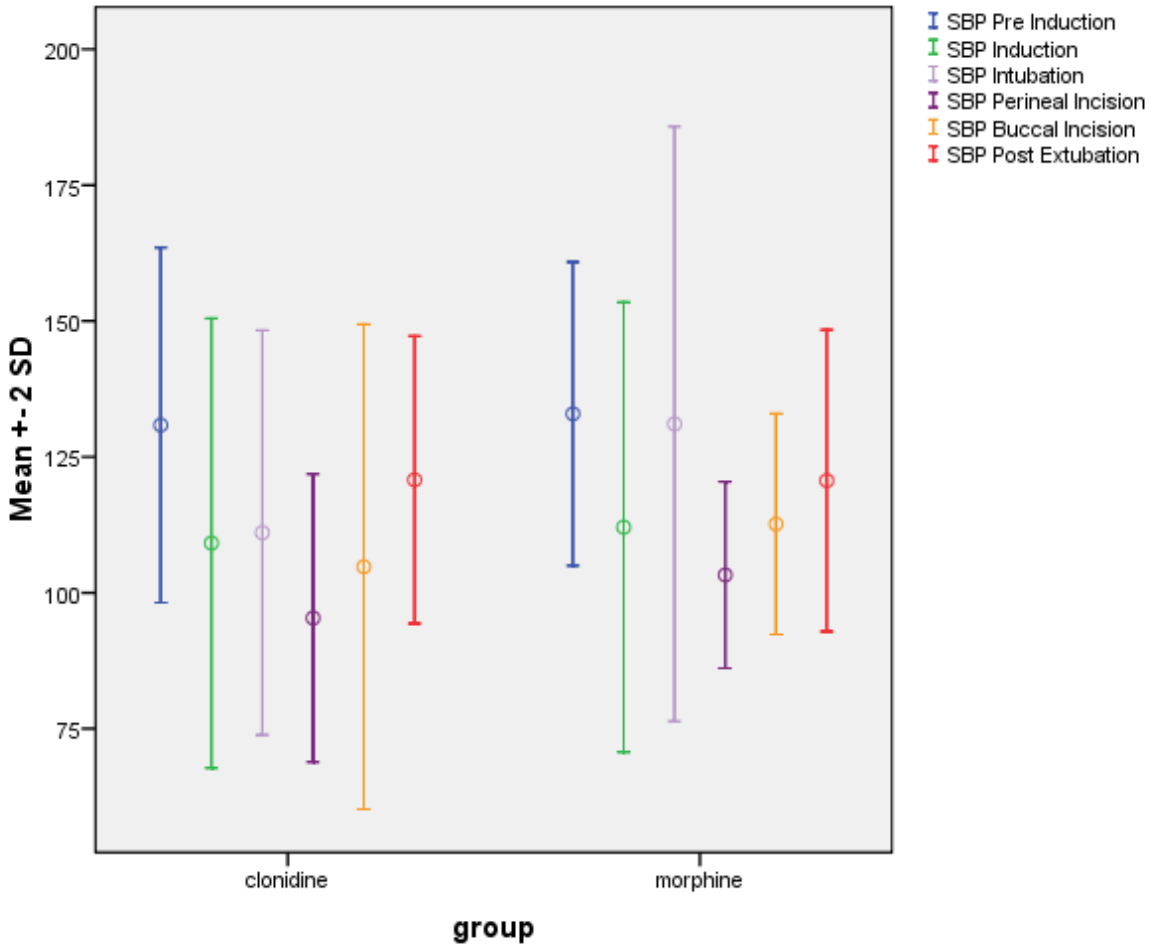
These variables were analysed to assess the hemodynamic stability in the two groups of patients.

SYSTOLIC BLOOD PRESSURE AT VARIOUS POINT OF TIME:

Table 7: This table shows the mean systolic blood pressure with standard deviation at various time intervals

	GROUP	Mean	S. D	P value
SBP Pre Induction	clonidine morphine	130.86 132.93	16.332 13.970	0.924
SBP Induction	clonidine morphine	109.14 112.07	20.680 20.697	0.685
SBP Intubation	clonidine morphine	111.07 131.07	18.611 27.371	0.006
SBP Perineal Incision	clonidine morphine	95.36 103.29	13.253 8.570	0.055
SBP Buccal Incision	clonidine morphine	104.79 112.64	22.310 10.142	0.241
SBP Post extubation	clonidine morphine	120.79 120.64	13.227 13.882	0.384

The baseline systolic blood pressure in clonidine and morphine was 87.9±17.4 and 84.86±17.074 mm of Hg. As the p value is 0.924 there is no significant difference in the baseline SBP between two groups.



Graph 4: Pictorial representation of changes in SBP at various point of surgery

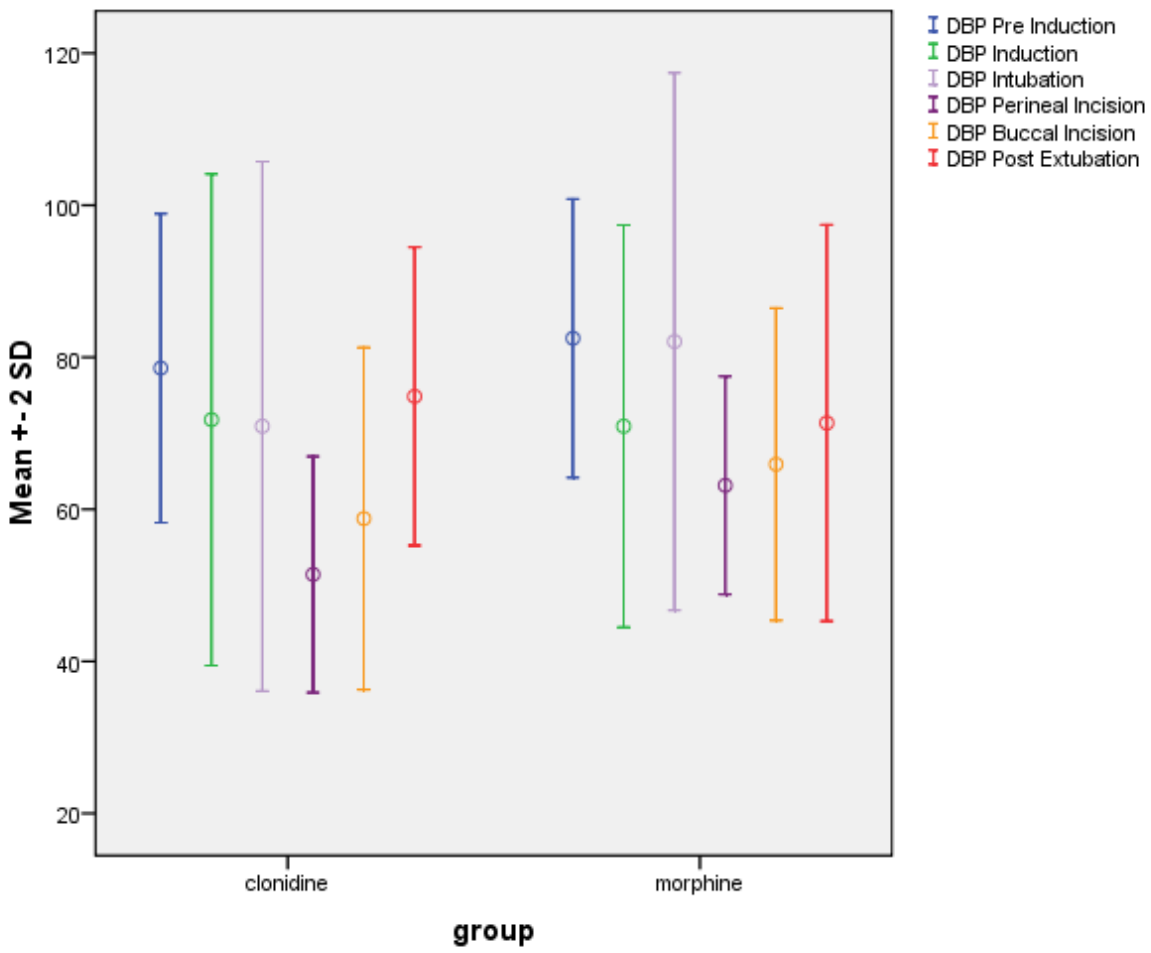
It represents increase in systolic blood pressure in morphine group at the time of intubation than the clonidine group. Therefore clonidine group has less intubation response to than morphine group (p value of 0.006).

DIASTOLIC BLOOD PRESSURE AT VARIOUS POINT OF TIME INTRAOPERATIVELY:

Table 8: This table shows the mean diastolic blood pressure with standard deviation at various time intervals during surgery.

	GROUP	Mean	S.D	P value
DBP Pre Induction	clonidine	78.57	10.166	0.523
	morphine	82.50	9.163	
DBP Induction	clonidine	71.79	16.163	
	morphine	70.93	13.229	0.875
DBP Intubation	clonidine	70.93	17.416	
	morphine	82.07	17.683	0.020
DBP Perineal Incision	clonidine	51.43	7.763	0.103
	morphine	63.14	7.167	
DBP Buccal Incision	clonidine	58.79	11.247	0.091
	morphine	65.93	10.269	
DBP Post Extubation	clonidine	74.86	9.813	
	morphine	71.36	13.030	0.658

The baseline DBP in clonidine and morphine was 78.5±10.1 mm of Hg and 82.5±9.16 mm of Hg. As the p value is 0.523 there is no significant difference in the baseline diastolic blood pressure in two groups.



Graph 5: Pictorial representation of changes in DBP at various point of surgery.

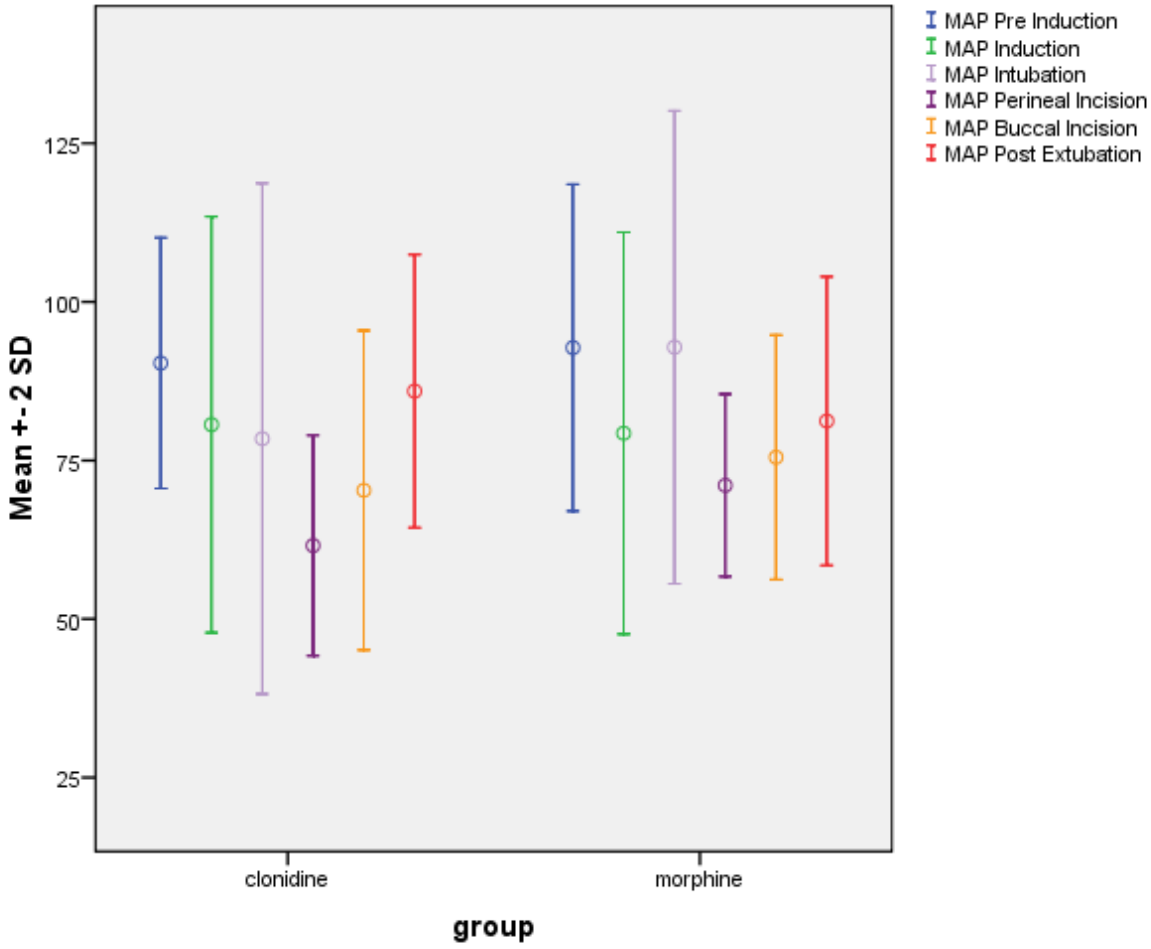
From this pictorial representation it can be noticed that there is significant increase in diastolic blood pressure in morphine group at the time of intubation. The p value of 0.02 signifies the blunting effect of clonidine on intubation response.

MEAN ARTERIAL PRESSURE AT VARIOUS POINT OF TIME INTRAOPERATIVELY:

Table 9: This table shows the mean of mean blood pressure with standard deviation at various time intervals

	GROUP	Mean	S. D	P value
MAP Pre Induction	Clonidine	90.36	9.881	
	Morphine	92.79	12.879	0.686
MAP Induction	Clonidine	80.64	16.397	
	Morphine	79.29	15.843	0.821
MAP Intubation	Clonidine	78.43	20.133	0.007
	Morphine	92.86	18.646	
MAP Perineal Incision	Clonidine	61.57	8.689	0.001
	Morphine	71.07	7.195	
MAP Buccal Incision	Clonidine	70.29	12.591	0.230
	Morphine	75.50	9.646	
MAP Post Extubation	Clonidine	85.93	10.759	0.197
	Morphine	81.21	11.376	

The baseline MAP in clonidine and morphine was 90.36±9.88 mm of Hg and 92.79±12.87 mm of Hg. As the p value is 0.686 there is no significant difference in the baseline Mean blood pressure in two groups.



Graph 6: Pictorial representation of changes in MAP at various points of surgery

Morphine group appears to have greater response to intubation and perineal incision. The change is statistically significant as p value is less than 0.05(0.007 and 0.001).This explains the better hemodynamic stability provided by clonidine during early intraoperative period.

TOTAL DOSE OF INTRAVENOUS FENTANYL USED INTRAOPERATIVELY:

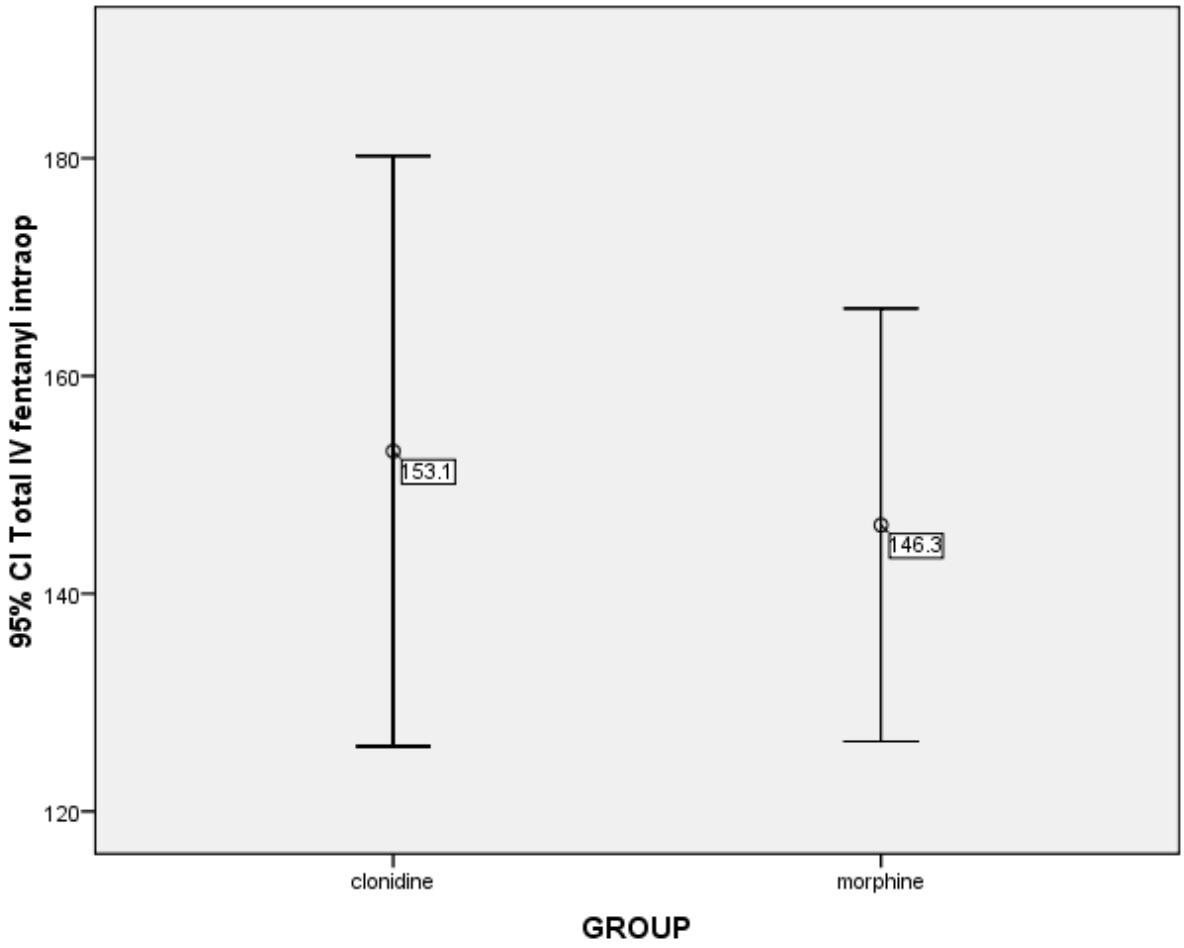
It gives an overview of total opioid required to maintain hemodynamic stability.

Table 10: This table shows the total intravenous fentanyl used during the surgery

GROUP	N	Mean (µgms)	S. D
Clonidine	21	153.10	59.571
Morphine	23	146.30	45.980

P value=0.673

The mean amount of total fentanyl used in clonidine group was 153±59.5 micrograms and 146±45.98 micrograms in morphine group. As the p value for the mean is 0.673 the difference is not significant.



Graph 7: Pictorial representation of total I.V fentanyl used during surgery

TIME BETWEEN STOPPING INHALATIONAL AGENT AND EXTUBATION:

Table 11: This table depicts the median and IQR of time between stopping inhalational agent and extubation.

	25thPercentile (in hours)	75thPercentile (in hours)	Median 50thPercentile (in hours)(IQR)
Clonidine N=21	0.10	0.15	0.12(0 .10-0.15)
Morphine N=23	0.12	0.25	0.15(.0.12-0.25)

P value: 0.024

This variable is analysed to see if whether there is any delay in extubation due to sedation effects of clonidine or morphine. There is no significant difference between the time between stopping inhalational agent and extubation.

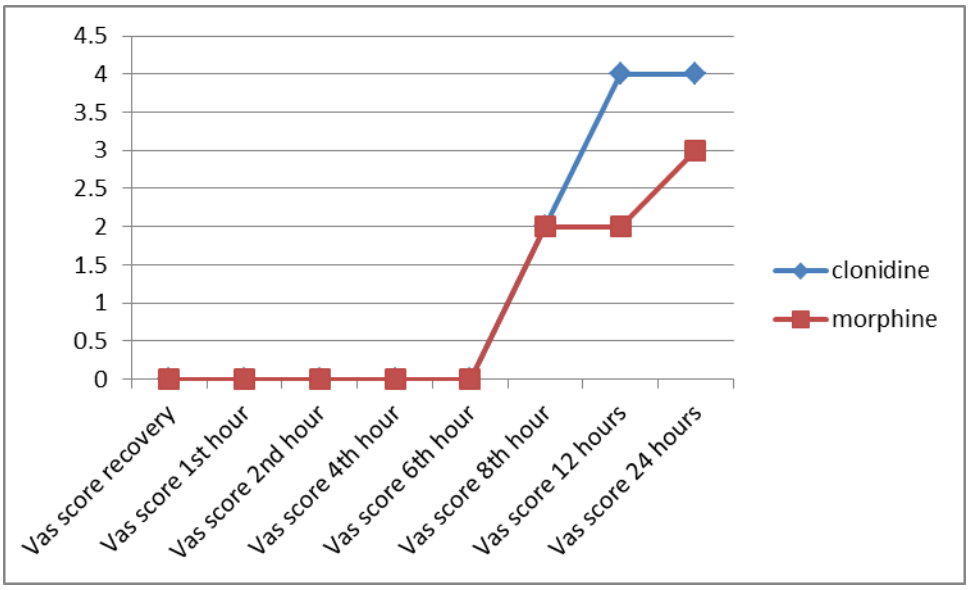
3) <u>POSTOPERATIVE PARAMETERS</u>:

VISUAL ANALOGUE SCORE (VAS) AT VARIOUS POINT OF TIME:

Table 12: This table shows the median perineal VAS scores at various time intervals in the post- operative period.

	Clonidine Median value(IQR)	Morphine Median value(IQR)	P value
VAS at 0hrs	0	0	1.000
VAS at 1hrs	0	0	1.000
VAS at 2hrs	0	0	0.295
VAS at 4hrs	0	0	0.484
VAS at 6hrs	0(0-2)	0(0-2)	0.547
VAS at 8hrs	2(1-4)	2(0-2)	0.178
VAS at 12hrs	4(2-4)	2(2-4)	0.307
VAS at 24hrs	4(2-4)	3(2-4)	0.216

Both the groups have shown onset of pain by approximately by 6th hour in the post-operative period.



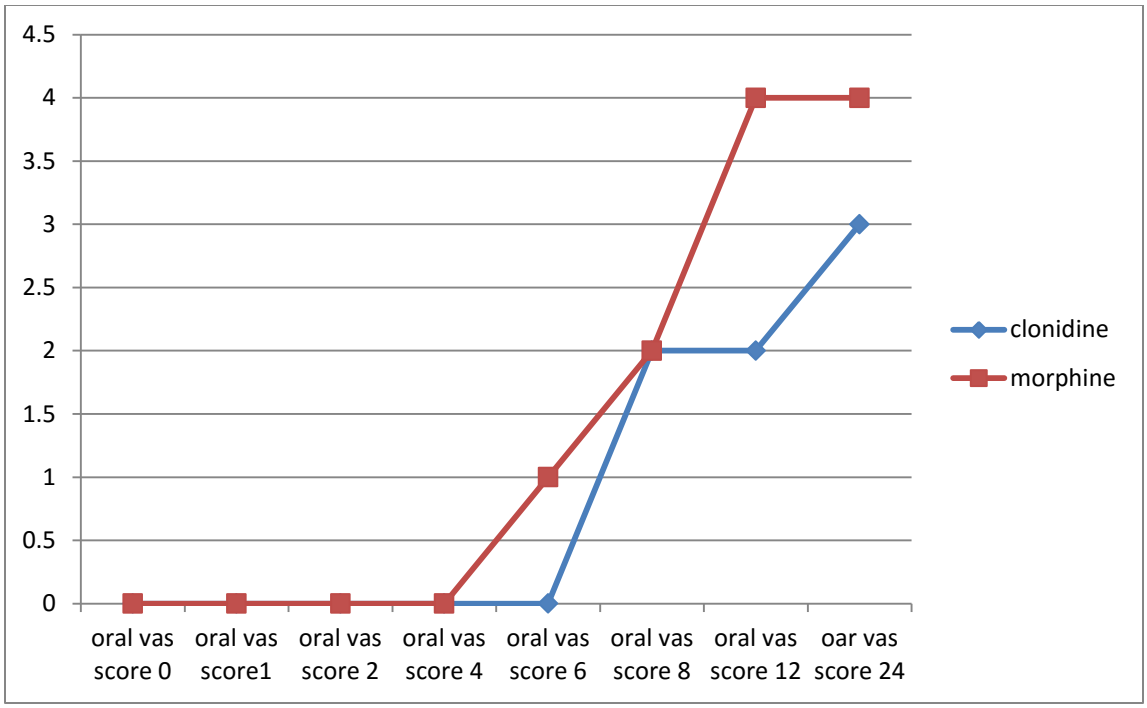
Graph 8: This graph shows the trend in VAS scores from the time of extubation.

VAS SCORE OF ORAL CAVITY AT VARIOUS POINT OF TIME:

Table 13: This table shows the median VAS score of buccal mucosa with standard deviation at various time intervals

Visual Analogue Score at (hours)	Clonidine Median value(IQR)	Morphine Median value(IQR)	P value
0	0	0	1.000
1	0	0	1.000
2	0	0	1.000
4	0	0(0-0.5)	0.704
6	0(0-2)	1(0-2.5)	0.648
8	2(1.5-4)	2.5(2-4)	0.421
12	2.5(2-4)	4(2-4)	0.186
24	3(2-4)	4(2-4.25)	0.179

The trend of onset of pain can be inferred from the data, which shows that morphine group complained of pain at the 4^{th} postoperative hour and the clonidine group at 6th postoperative hour.



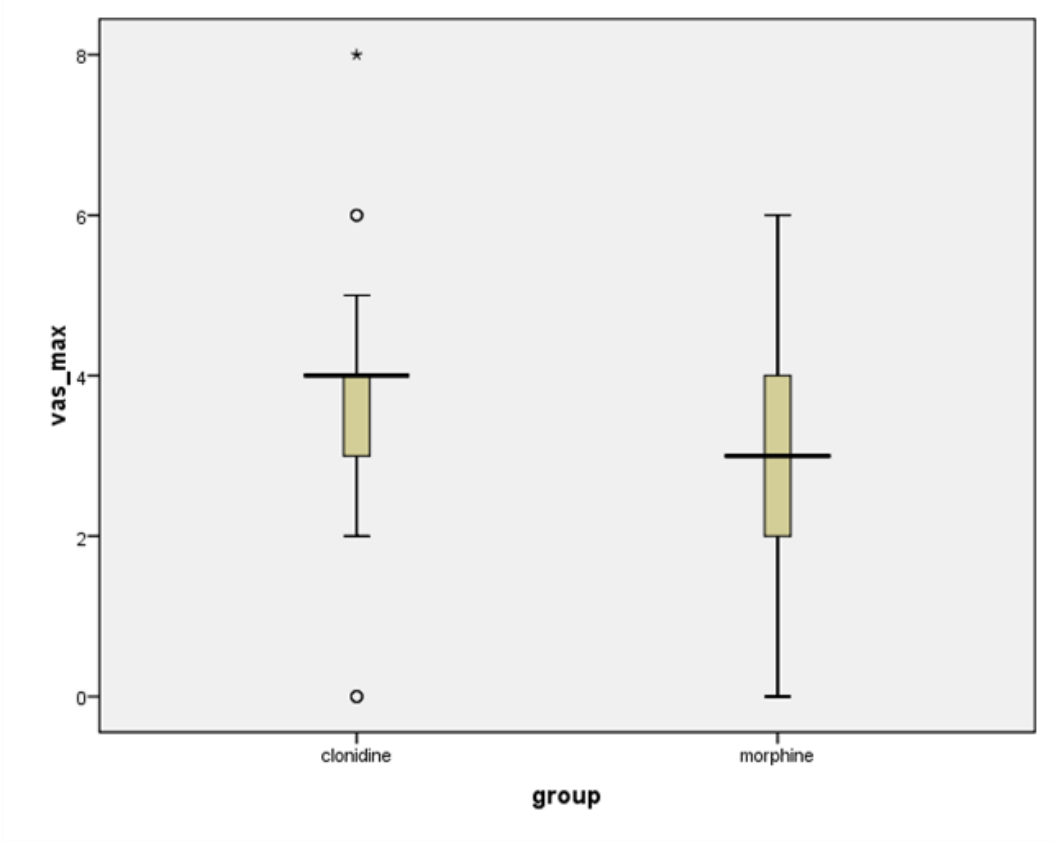
Graph 9: This graph shows the trend in buccal mucosal VAS scores from the time of extubation.

HIGHEST PERINEAL VAS SCORE:

The highest VAS score was analysed to find out the intensity of pain in both groups over a period of 24hours.

Table 14: This table shows the highest perineal VAS score in two groups at different time intervals.

Highest perineal VAS score at (hours)	Clonidine (Median)	Morphine (Median)
0	0	0
1	0	0
2	0	0
4	0	0
6	0	0
8	2	2
12	4	2
24	4	3



Graph 10: Pictorial depiction of highest perineal VAS score in two groups.

The highest VAS score in clonidine group over a period of 24 hours was 4(median value, 25th percentile-2.5 and 75th percentile-4) and in the morphine group it was 3(median value, 25th percentile-2 and 75th percentile-4). The above given values are run through Mann-Whitney test. The resultant p value is 0.1, so this difference has no statistical significance.

HIGHEST BUCCAL VAS SCORE:

The highest buccal mucosal VAS score was analysed to find out the analgesic effect of both drugs on buccal mucosa over a period of 24 hours

Table 15: This table shows the highest buccal VAS score in two groups.

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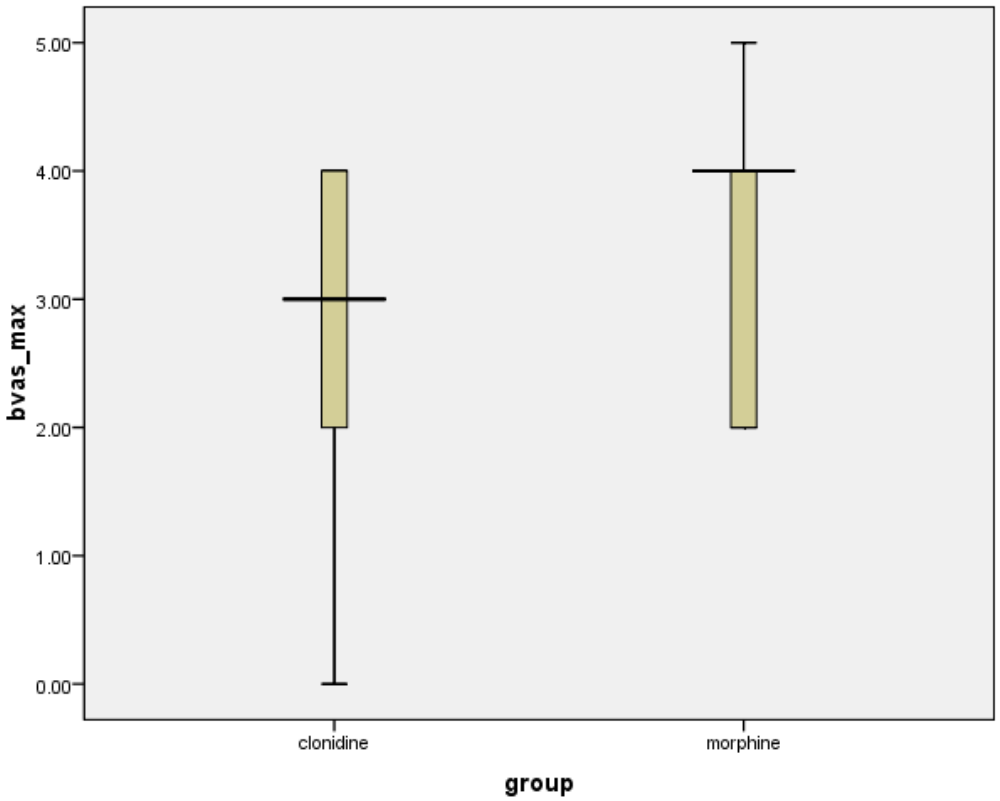
Highest Buccal VAS score At (hours)	Clonidine (Median)	Morphine (Median)
0	0	0
1	0	0
2	0	0
4	0	0
6	0	0
8	2	2
12	4	2
24	4	3



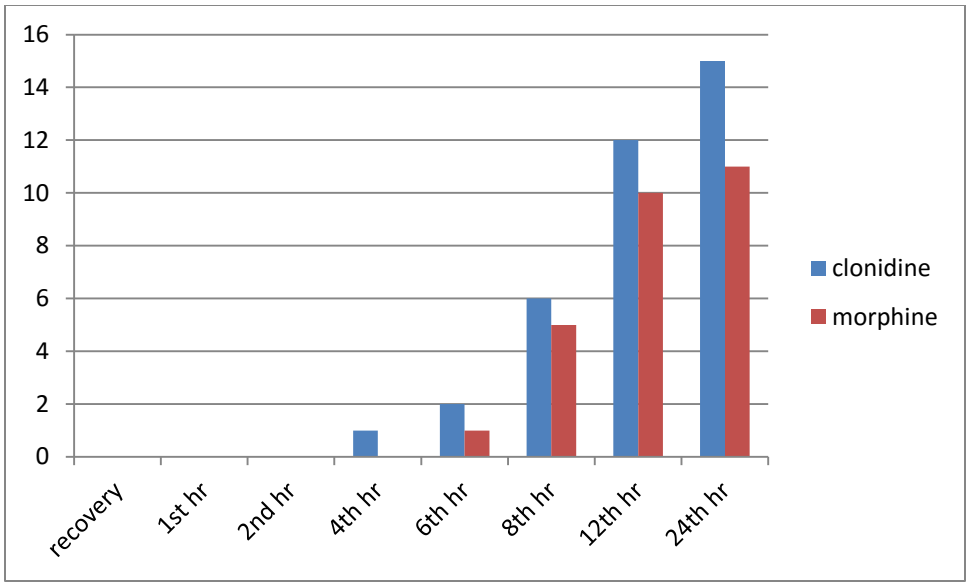
Graph 11: Pictorial depiction of highest buccal VAS score in two groups.

The highest VAS score in clonidine group over a period of 24 hours was 3(median value, 25th percentile-2 and 75th percentile-4) and in the morphine group it was 4(median value, 25th percentile-2 and 75th percentile-4). The above given values are run through Mann-Whitney test. The resultant p value is 0.2, so this difference has no statistical significance**.**

TIME FOR RESCUE ANALGESIA:

Table 16: This table shows the time to rescue analgesia in two groups

	Clonidine N=21 Number of patients / (%)	Morphine N=21 Number of patients / (%)
At Recovery	0	0
1st post-op hour	0	0
2nd post-op hour	0	0
4th post-op hour	1(4.8%)	0
6th post-op hour	2(9.5%)	1(4.3%)
8th post-op hour	6(28.6%)	5(21.7%)
12th post-op hour	12(57.1%)	10(43.5%)
24th post-op hour	15(71.4%)	11(47.8%)



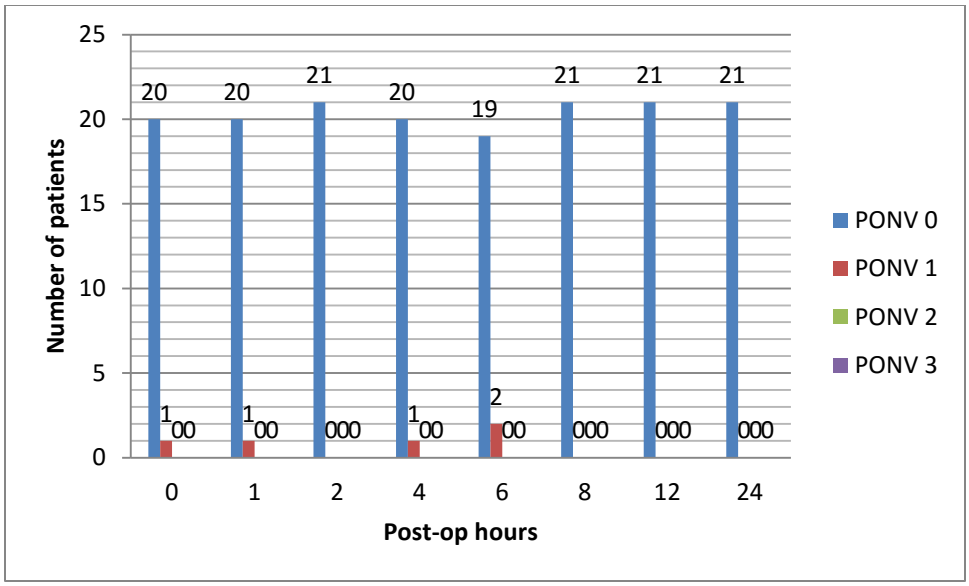
Graph 12: Pictorial representation of time to rescue analgesia in two groups.

It is evident that clonidine group started to get rescue analgesia by 4th post-operative hour and morphine group by 6th post-operative hour. By the end of 12th post-operative hour more than 50% of clonidine group patients received rescue analgesia.

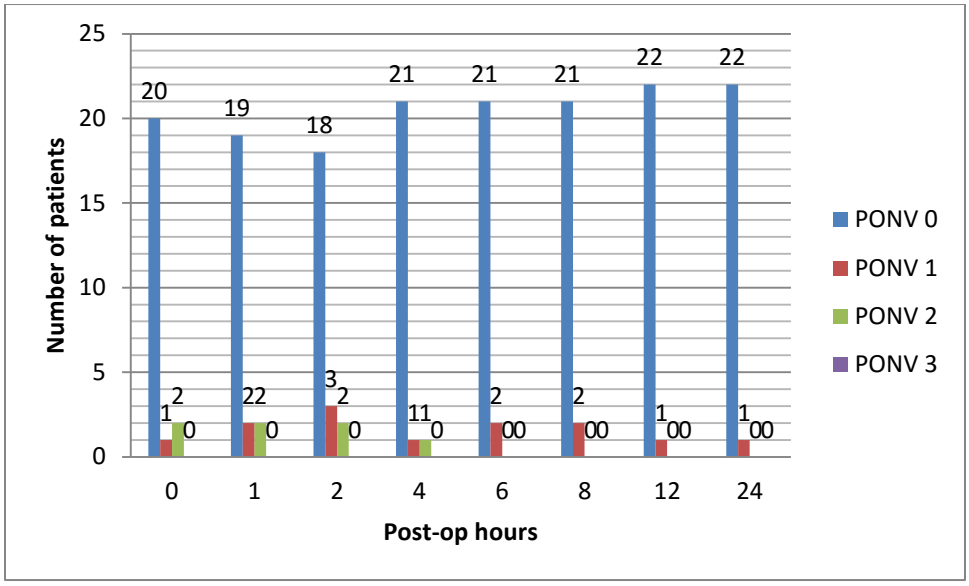
POST OPERATIVE NAUSEA AND VOMITING SCORE AT VARIOUS POINTS OF TIME:

Table 17: This table shows the median PONV scores at various time intervals in the postoperative period.

	Clonidine Median value(IQR)	Morphine Median value(IQR)	P value
PONV at 0hrs	0	0	0.322
PONV at 1hrs	0	0	0.179
PONV at 2hrs	0	0	0.025
PONV at 4hrs	0	0	0.591
PONV at 6hrs	0	0	1.000
PONV at 8hrs	0	0	0.172
PONV at 12hrs	0	0	0.339
PONV at 24hrs	0	0	0.339



Graph 13: Pictorial representation of PONV scores at various in the post-operative period in clonidine group.



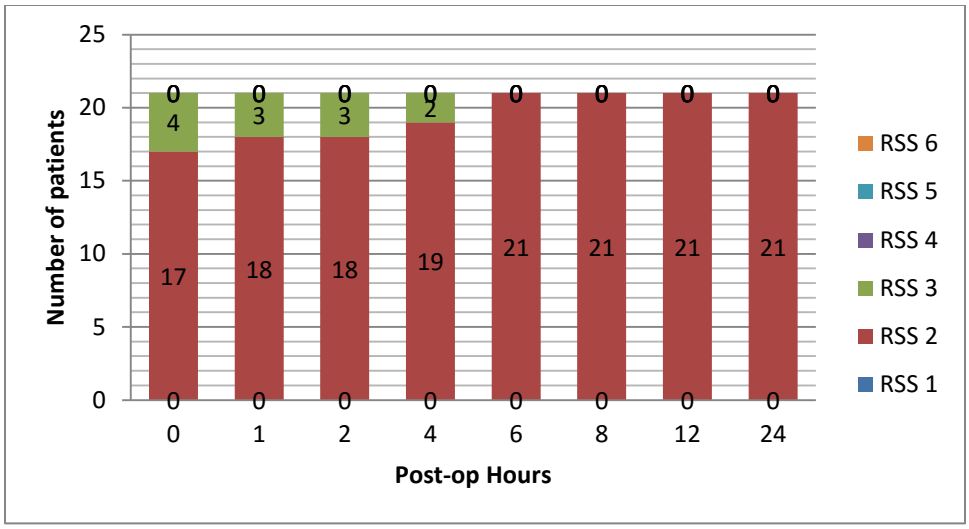
Graph 14: Pictorial representation of PONV scores at various in the post-operative period in morphine group.

From the above graph it can be identified that three patients in morphine group and one patient in clonidine group had PONV score more than 0. However it is not statistically significant(p value=0.288).The statistical method used for the group comparison is repeated measures analysis of variance(ANOVA) and test statistic used is Greenhouse Geisser test statistic.

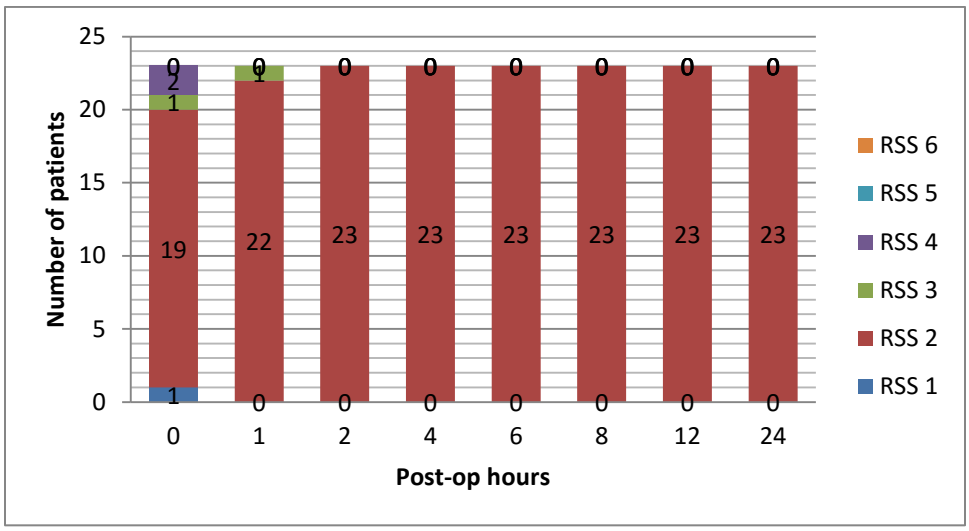
POST OPERATIVE SEDATION AT VARIOUS POINTS OF TIME:

Table 18: This table shows the median Ramsay sedation score at various time intervals

Ramsay sedation score At (hours)	Clonidine Medianvalue (IQR)	Morphine Median value(IQR)	P value
0	2	2	0.506
1	2	2	0.258
2	2	2	0.063
4	2	2	0.134
6	2	2	1.000
8	2	2	1.000
12	2	2	1.000
24	2	2	1.000



Graph 15: Pictorial representation of Ramsay sedation score in clonidine group.



Graph 16: Pictorial representation of Ramsay sedation score in morphine group.

The above graph depicts that 4 patients in clonidine group and 3 patients in morphine group has Ramsay sedation score more than 2. However it is not statistically significant(p value=0.450).The statistical method used for the group comparison is repeated measures analysis of variance(ANOVA) and test statistic used is Greenhouse Geisser test statistic.

TIME BETWEEN EXTUBATION AND ORAL INTAKE:

Table 19: This table shows the mean with standard deviation of time between extubation to oral intake

GROUP	N	Mean(hours)	S. D
Clonidine	21	7.0195	3.82921
Morphine	23	5.7857	2.41261

P value=0.215

There is no significant difference between two groups in first oral intake in the post-operative period.

TIME BETWEEN EXTUBATION AND MOBILIZATION:

Table 20: This table shows the mean duration between extubation and mobilisation

GROUP	N=	Mean(in hours)	S.D
Clonidine	21	17.8652	3.80504
Morphine	23	15.8813	4.13751

The mean duration of mobilisation in the postoperative period in clonidine group is 17.8±3.8hrs and 15.8±4.1hrs in morphine group. The difference is statistically insignificant as p value is 0.105. Table 12: It shows the median Ramsay sedation score at various time intervals

DISCUSSION

Urethroplasty, a surgical repair is attempted as corrective measure in the male urethra for urethral stricture after conservative and non-surgical methods does not produce the desired patient satisfaction.

The perineal region is an area supplied with a profuse sensory nervous supply. Surgical procedures to the region may produce severe pain in the post-operative period.

The study was aimed at comparing two well accepted modes of postoperative analgesia, i.e., intrathecal morphine and intrathecal clonidine to ascertain which would produce better and longer post-operative analgesia (28) (43). This was also done to ascertain the extent of known side effects of these additives to spinal analgesia.

Often the buccal mucosa is harvested to replace the damaged urethral mucosa. The added pain from the buccal donor site also adds to the postoperative pain. Our aim was to also determine whether the use of additives to spinal analgesia would cause a decrease pain in the oral cavity.

In this randomized control double blinded study, 46 patients were recruited, two patients had no surgical intervention done and hence 44 patients were only analysed.

The demographic profiles of the patients in both the arms of the study were comparable. The population predominantly consisted of middle aged men (the mean age was 40 years between both groups).This demographic profile was comparable to the patient population

selected by Gecaj-Gashi et al study looking at the use of intrathecal clonidine for trans urethral surgery (6).

Duration of surgery as a consideration, median value of duration of surgery in clonidine and morphine group was 4.0(3.15-5.50) hours and 4.00(3.00-5.00) hours. There was no significant difference between the two groups (p value=0.407).

Comparison of the hemodynamic parameters between the two groups at various points of time during the intraoperative period was measured to look at response to surgery and side effects of the adjuncts with bupivacaine. Heart rate and blood pressure parameters had a significant less response to intubation and skin incision at the perineum with the clonidine group (P value is <0.05). This may be attributed to the early onset of action of clonidine and its central sympatholytic effect. This is comparable to the study by Sethi B. et al in which intrathecal clonidine 1micro gram per kg body weight was given to patients undergoing abdominal surgery (25)(44). However, when analysing the response to the buccal mucosa harvest these parameters were not different between the groups. This lack of differential response may be explained by the delayed rostral spread of these adjuncts to Bupivacaine 10 mg. The hemodynamic response to extubation was comparable. Two patients in clonidine group have decrease in heart rate (decrease of 20 beats per minute) at the time of perineal incision which was treated with anticholinergic drugs. But it is statistically insignificant (P value=0.2) Three patients in clonidine group have significant decrease in diastolic blood pressure (decrease of 30 mm of Hg) which

was treated with phenylephrine and ephedrine. It can be compared with the study done by Yoganarasimha et al.in patients undergoing lower abdominal surgeries.(5)

The use of intravenous fentanyl consumption was compared. The mean of total fentanyl used in clonidine group was 153+_59.5 micrograms (2.5 µgms/Kg body weight) and 146+_45.98 micrograms (2.2 µgms/Kg body weight) in morphine group was marginally more with clonidine. However the difference was not significant (p value is 0.673).

The observations of the postoperative pain scores were divided between the patient's perception of perineal site pain and buccal mucosa donor sites. Significant pain was defined as a VAS at or above 4 when the patient would be administered rescue analgesia on demand. Perineal site pain started to trend upwards by the 12^{th} hour and highest VAS was 4. The Clonidine group had a VAS of 4 by the 8^{th} hour and remained persistent during the duration of observation. The morphine group had a highest pain score of 2, which remained constant for the period of observation. Contrary to expectation the VAS score at the buccal mucosa donor site showed an early trend to increased VAS within the morphine group. Morphine group had significant pain score of 4 by the 8^{th} postoperative hour and remained persistent, while the clonidine group did not have significant donor site pain for the duration of the study. Studies done in the past have shown the mean duration of postoperative analgesia in clonidine group is around 8-10hours(6) (43) whereas morphine provides analgesia for 24 hours(3). It was found that more than 50% patients in clonidine group received rescue analgesia by 12th post-operative hour though a few number of patients received additional analgesics by 4th post-operative hour. In the

morphine group at 12 hours 43% of patients requested for rescue analgesia and a few number of patients received by 6th post-operative hour. At the end of observation period of the study 71.4% had rescue analgesia in the clonidine group as compared to 47.8% in the morphine group.

The median time to extubation after stop of inhalation was 12 minutes in the clonidine arm and 15 minutes in the morphine arm, which was similar to the observation by Yaguchi et al by using two different doses of oral clonidine for premedication and assessing the extubation time after stop of volatile anaesthesia (39). Neither of these drugs administered intrathecally prolonged the awakening time after anaesthesia.

The Ramsay sedation score showed a moderately higher sedation among the patients who received clonidine in the first four hours as compared with the morphine however the difference was not statistically significant and the maximum sedation score was two.

Postoperative nausea and vomiting is a consequence of opioid receptor stimulation of the dopaminergic receptors of the chemo trigger zone. PONV of score of maximum of 2 was recorded in two patients during the 24 hour period. PONV score of 1 was present up to the first four hours in the clonidine group. Inspite of the presence of PONV there was no significant difference in time between extubation and first oral intake and mobilization between the two groups.

The randomized controlled trial between the use of clonidine and morphine as adjuncts to 10mg of hyperbaric bupivacaine spinal anaesthesia in combination to spinal anaesthesia brought a few observations.

Primarily, clonidine had significantly better intraoperative hemodynamic response to sympathetic response to painful stimulation during intubation and skin incision when compared to morphine. However, the postoperative period morphine had a better pain relief, considering that clonidine group requested for rescue analgesia as early as 4 hours post operatively. Despite the better perineal pain relief, the onset of pain at the buccal mucosal donor site was earlier with the morphine group. Morphine provided a moderately longer duration of pain relief compared to clonidine. This could possible because of the central alpha 2 agonist activity of clonidine (30). Side effects of both drugs, i.e., bradycardia, hypotension, sedation and PONV were minimal.

CONCLUSION

1) In conclusion intrathecal clonidine is as effective as intrathecal morphine in providing analgesia during the first 12 hours postoperative hours among patients undergoing urethroplasty surgery.
2) In patients who underwent substitution urethroplasty using buccal graft the onset of oral cavity pain is later in clonidine group.
3) Clonidine provides better hemodynamic stability during laryngoscopy as compared to morphine (statistically significant).
4) Intrathecal clonidine has less incidence of PONV, though statistically insignificant.
5) There is no significant difference between intrathecal clonidine (1microgram per kg) and intrathecal morphine (3 micrograms per kg) for postoperative sedation.
6) There was no difference in the total amount of fentanyl used in the intraoperative period to supress the stress response in both group.
7) Extubation time is similar in both the groups.

LIMITATIONS

1) The sample size was inadequate to assess the effect of intrathecal morphine and clonidine on buccal mucosal pain. A large sample size may have shown a statistically significant outcome for buccal mucosal VAS score between the two groups at various point of time.
2) The use of patient control analgesic regime may have been a better tool in the post- operative analgesic management and in the assessment of total analgesic requirement over 24hours.
3) A large sample size may be required to bring out a statistical significance between both the groups for time to rescue analgesia.

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ANNEXURES

1) INFORMATION SHEET
2) INFORMED CONSENT
3) DATA COLLECTION PROFORMA
4) DRUG SAFETY MONITORING BOARD REPORT
5) DATA SHEET

INFORMATION SHEET:

STATEMENT ABOUT THE RESEARCH

The Department of Anaesthesiology, CMC Vellore and the department of urology , CMC Vellore are undertaking this research project to compare two different pain relieving medicines morphine and clonidine placed intrathecally in subjects undergoing urethroplasty surgery for urethral stricture. This is to ascertain if there is reduction in pain after surgery and also to see whether they have any increased side effects as drowsiness, nausea and vomiting and delayed mobilization after surgery.

The subject's participation in this research study is voluntary. Refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled and there will be no compromise in the quality of care the subject receives. The subject can choose to withdraw from the study at any time it will not involve any penalty or loss of benefits to which the subject is otherwise entitled. Adequate measures will be taken to maintain the confidentiality of the subject's identity and the data collected. Only those directly involved in the research will access the data as and when required.

1.WHAT IS URETHROPLASTY SURGERY?

The urethra is an important part of the urinary tract. It's primary function is to pass urine outside the body, this channel also has an important role in ejaculating semen from the reproductive tract of men. A urethral stricture is a scar in or around the urethra, which can block the flow of urine, and is a result of inflammation, injury or infection.Male

urethral stricture disease is prevalent and has a substantial impact on quality of life and health. Management of urethral strictures is complex and depends on the characteristics of the stricture. Urethral strictures are managed initially by urethral dilation and internal urethrotomy. For both of these procedures, the risk of recurrence is greater for men with longer strictures, penile urethral strictures, multiple strictures, presence of infection, or history of prior procedures. Long-term success rates are higher for surgical reconstruction with urethroplasty, with most studies showing success rates of 85–90%.

2. HOW WILL THE SUBJECT BE ANAESTHETISED FOR THIS SURGERY?

The whole process of anaesthesia will be conducted by experienced and qualified doctors in the field of anaesthesia. The subject is made unconscious using medicines given through the blood and using gases which keep the subject unconscious. Medicines for pain relief will be injected around the spinal cord . The functioning of the heart and vital organs will be constantly evaluated throughout by standard monitoring devices attached to the subject's body which ensures immediate detection and management of any untoward incident. Breathing will be supported by sophisticated machines(ventilators) through the entire period of anaesthesia. The subject will regain consciousness within few minutes of completion of the surgery.

3.WHY IS THIS RESEARCH DONE?

Perineum has rich nerve supply, hence patients experience pain during surgery and after surgery. During surgery increase in blood pressure and pulse. This rise in blood pressure

and pulse is harmful for the subject. In usual practice to reduce this blood pressure higher doses of anaesthetic medicines and other medicines to reduce blood pressure is given. This delays the process of regaining consciousness after the surgery. Injecting pain relieving medicines into the fluid around the spinal cord before starting the surgery prevents this increase in blood pressure and heart rate. Routinely morphine is used for this purpose, however there is no study done to see the efficacy of clonidine during this surgery which has lesser sedative and nausea and vomiting side effects . At the end of the research if the beneficial effect is proved, usage of this drug can be included into the anaesthetic management of these surgeries in future and the information derived out of this research will be beneficial for medical science at large.

4.HOW WILL THIS RESEARCH BE DONE?

The participant will be participating in a randomised controlled research project. This is done when we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To ensure that the groups are the same, each participant is put into a group by chance (random). Around 50 subjects need to be studied in order to make valid conclusions. The 50 subjects will be arbitrarily assigned to two groups based on allocation done by a computer and hence neither the investigating doctor nor the subject can decide which group the subject is going to be in. In one group medicine 1 (morphine 3mcg/kg) and in the other group medicine 2 (clonidine 1mcg) will be injected in to the fluid around the spinal cord under

strict aseptic conditions. After the subject is anaesthetized blood pressure and heart rate are measured continuously. The observations will be made at regular intervals to collect the necessary data for the research. The subject will be asked at multiple occasions to tell about the intensity of pain felt after surgery for 24hrs.

5. WHAT ARE THE THINGS THE SUBJECT IS EXPECTED TO DO AS A PART OF THIS RESEARCH?

The subject is expected to express his intensity of pain as a score in a scale ranging from 0 to 10 with 0 being no pain and 10 being very severe pain. This has to be done 1hr, 2hrs, 4hrs, 6hrs, 8hrs, 12 hrs,24hrs after operation. The subject is expected to cooperate with the doctor who will be assessing this pain score.

6. HOW LONG WILL A SUBJECT NEED TO BE A PART OF THIS RESEARCH?

The subject needs to be a part of this research only for one days; the day of the surgery and 24hrs after the surgery is over. There is no extra day of stay required in the hospital for the sake of research or any extra visit to hospital required.

7. WHAT IS MORPHINE AND CLONIDINE?

Morphine is opioid drug which causes pain relief This is the most commonly used drug today. It is a safe drug when used within the allowed dose. Clonidine is a different group of drug(alpha2 agonist) which is now being widely used and is considered to be safer when used with in the allowed dose.

8. IS THERE ANY RISK FOR THE SUBJECT BECAUSE OF THE RESEARCH?

Both Morphine and Clonidine are drugs which are widely used and considered very safe when used within the recommended dose. With high doses of this drug in the blood it can cause respiratory depression and heart dysfunction. But in the study we are doing, the dose of this drug is much less than the maximum allowed dose. In addition, our set up is capable of treating any such complications , if they occur.

9. WILL THERE BE ANY DISCOMFORT FOR THE SUBJECT?

This spinal injection will be given after injecting local anaesthetic medicine, which makes skin and underlying structures numb ,hence subject has mild discomfort.

10. WILL THE SUBJECT HAVE ANY ADVANTAGE OR BENEFIT BECAUSE OF PARTICIPATING IN THE STUDY?

There will not be any added advantage for the subject in terms of money or care given because of participation in this research.

INFORMED CONSENT:

Study Title: Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this

access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) .

(v) I agree to take part in the above study.

(vi)I am aware of the Audio-visual recording of the Informed Consent.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

DATA COLLECTION PROFORMA:

Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.

DATA COLLECTION PROFORMA:

SERIAL NO: DATE:

PATIENT NAME:

HOSPITAL NO: AGE: YRS ASA: 1/2

HEIGHT: CMS WEIGHT: KG BMI:

DURATION OF SURGERY: HRS

TIME OF INTRATHECAL INJECTION OF DRUG : TIME OF INCISION:

TOTAL IV FENTANYL INTRAOP:

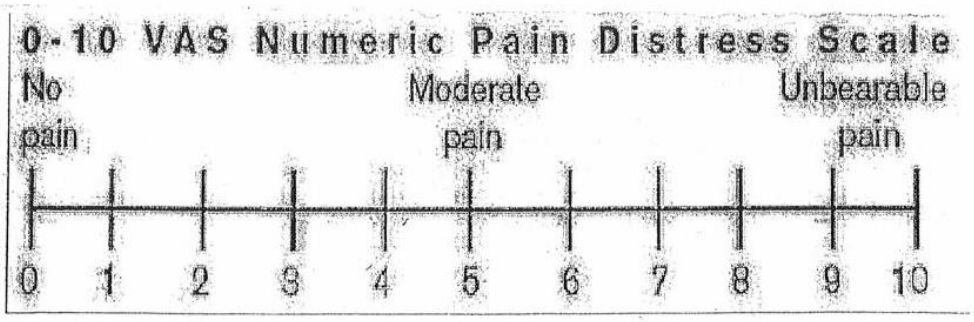
	PRE INDUCTION	INDUCTION	INTUBATION	PERINEAL INCISION	BUCCAL INCISION	POST EXTUBATION
HR						
SBP						
DBP						
MAP						

TIME OF STOPING INHALATIONAL AGENT : TIME OF EXTUBATION :

	RECOVERY	1st hr	2nd hr	4th hr	6th hr	8th hr	12hrs	24 hrs
VAS SCORE								
RAMSAY SEDATION SCORE								
PONV								

TIME FOR FIRST ORAL INTAKE: TIME FOR MOBILIZATION:

	RECOVERY	1st hr	2nd hr	4th hr	6th hr	8th hr	12hrs	24 hrs
VAS SCORE								
RAMSAY SEDATION SCORE								
PONV								



RAMSAY SEDATION SCORE:

- Anxious, agitated, restless -1
- Cooperative, oriented, tranquil-2
- Responsive to commands only-3

If Asleep :

- Brisk response to light glabellar tap or loud auditory stimulus-4
- Sluggish response to light glabellar tap or loud auditory stimulus-5
- No response to light glabellar tap or loud auditory stimulus-6

PONV:(patient evaluation and investigator observes)

- No nausea and not vomiting-0
- Light nausea or vomiting without previous nausea-1
- Moderate nausea and/or vomiting -2
- Severe nausea and/or reoccurring vomiting-3

DRUG SAFETY MONITORING BOARD REPORT:

OFFICE OF THE VICE-PRINCIPAL (RESEARCH)
CHRISTIAN MEDICAL COLLEGE, VELLORE – 632 002

1st June 2015

Dr. Geetha Bhavani Gullipalli,
PG Registrar,
Department of Anaesthesiology,
Christian Medical College, Vellore

Ref: **IRB. Min. No:** 9178 dated 26-Nov-2014

Dear Dr. Geetha Bhavani Gullipalli,

The Data Safety Monitoring Board (DSMB) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "*Intrathecal morphine or clonidine for postoperative analgesia in patients undergoing urethroplasty- a comparison.*" on 15th May 2015 in the Seminar Room, Asha building, Christian Medical College & Hospital, Vellore 632 004.

The Committee reviewed and discussed the following

1. No major issues.

Dr. Geetha Bhavani Gullipalli and Dr. Tony Thomson Chandy were present during the meeting and satisfactorily responded to the queries raised by the Members.

The Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded

from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmchvellore.edu/static/research/Index.html.

Thank you.
Yours Sincerely,

Dr. Nihal Thomas,
Addl. Vice Principal (Research) & (Convener) Data Safety Monitoring Board - DSMB

CC: Dr. Tony Thomson Chandy, Professor,Anaesthesiology,CMC

Telephone: +91 (0) 416 228 4294
Email: research@cmcvellore.ac.in / researchothers@cmcvellore.ac.in

DATA SHEET:

idno	hno	age	sex	ht	wt	bmi	Uno thrs	dos	timedrug	Time drug1	timelnd	Tim elncl1	Bet Drug	lvten	lmpnelnd	hrbd	hrbt	hrperl	hrbuccal
1	683541g	23	1	161	65	25.08	1	5	1.5	pm	2.1	pm	0.2	145	93	68	76	76	74
2	036323g	27	1	174	67	22.13	2	4	1.4	pm	2.25	pm	0.25	150	99	92	98	71	74
3	1103832g	59	1	160	67	26.17	1	3.3	3	pm	3.54	pm	0.54	100	67	67	78	55	74
4	1259811g	28	1	170	47	16.26	1	4.3	11.3	am	12.1	pm	0.4	100	80	82	57	57	74
5	1235398g	23	1	170	70	24.22	1	4	7.45	am	8.3	am	0.45	100	75	69	90	61	74
6	0848332g	35	1	165	67	24.61	1	6	2.15	pm	3.15	pm	1	200	82	62	80	65	80
7	4956020f	50	1	170	65	22.49	2	8.3	8.1	am	9.07	am	0.57	200	90	90	94	81	80
8	8623099f	36	1	183	78	23.29	1	1.45	11.59	Am	12.1	pm	0.11	100	87	71	108	85	81
9	1154490g	44	1	165	65	23.88	2	6.15	1.2	Pm	2.12	pm	0.52	150	74	86	74	72	81
10	1611958g	48	1	168	68	17.01	2	7	10.55	Am	11.4	am	0.45	200	76	57	78	54	61
11	8722300f	47	1	165	64	23.51	1	2.3	12.2	Pm	12.4	pm	0.2	100	83	84	88	62	61
12	1284719g	61	1	162	62	23.62	2	4	2.45	Pm	3.25	pm	0.4	100	90	39	90	71	86
13	7404710f	37	1	158	59	20.03	1	4.3	2.2	Pm	2.5	pm	0.3	100	115	116	85	69	69
14	1521778g	47	1	167	80	28.69	2	3	1.3	Pm	2.15	pm	0.45	200	91	75	87	67	70
15	1614054g	19	1	165	45	16.53	1	4	12.15	Pm	1	pm	0.45	175	102	98	112	60	
16	1568675g	34	1	163	59	22.48	2	4	12.4	Pm	1.15	pm	0.35	120	88	94	91	63	58
17	1175958g	26	1	155	70	29.14	2	3.3	7.35	Am	8.25	am	0.5	150	72	81	97	73	78
18	1294044g	48	1	168	66	23.38	2	2.15	4.15	Pm	4.45	pm	0.3	150	86	88	92	78	77
19	8904487f	38	2	159	65	25.71	1	2.5	7.3	Am	7.45	am	0.15	100	91	83	94	97	
20	9482757f	30	1	160	60	23.44	2	6.5	9.45	Am	10.3	am	0.45	240	85	82	90	91	85
21	8468502d	38	1	175	80	26.12	2	3.3	1.55	Pm	2.1	pm	0.15	100	65	107	117	74	86
22	1075533g	28	1	168	64	22.68	2	2.5	3.45	Pm	4.25	pm	0.4	180	86	82	74	63	60
23	1818888g	29	2	162	42	16	2	3	7.35	Am	8.25	am	0.1	120	98	99	100	69	82
24	0177459g	36	1	169	64	22.41	1	4	12.35	Pm	1.35	pm	1	100	88	87	86	50	
25	1700138g	39	1	157	50	20.28	2	4.15	3.52	Pm	4.22	pm	0.3	170	103	76	90	72	90
26	2062778g	38	1	163	58	22.1	2	5	12.45	Pm	1.4	pm	0.55	200	80	70	92	68	64
27																			
28	2632564g	46	1	170	75	25.95	2	4	2.35	Pm	2.55	pm	0.3	100	67	64	80	73	71
29	2072256g	60	1	165	53	19.47	2	4	4.35	Pm	5.3	pm	0.55	150	75	75	77	74	80
30	1567256g	43	1	166	69	25.04	2	4.3	2.38	Pm	3.1	pm	0.42	300	83	73	75	64	66
31	2215418g	42	1	172	66	22.31	2	2.4	9.38	Am	10.1	am	0.42	225	98	92	94	119	121
32	1330828g	50	1	160	74	28.91	2	6.3	2.15	Pm	2.5	pm	0.35	290	132	106	95	73	92
33	183552g	62	1	165	66	24.24													
34	2184658g	54	1	163	49	18.44	1	3.3	1.15	Pm	1.35	pm	0.2	140	75	72	78	69	
35	2195403g	32	1	170	70	24.22	2	6	12.4	Pm	1	pm	0.2	200	81	72	61	63	94
36	8763196f	41	1	169	48	16.81	1	4	3.15	Pm	3.45	pm	0.3	100	63	70	55	61	
37	1469852g	39	1	176	65	20.98	2	4.45	3.35	Pm	3.5	pm	0.35	125	84	64	64	60	90
38	8653838f	31	1	168	70	24.8	2	1.55	3.15	Pm	3.5	pm	0.35	100	102	75	81	86	80
39	2114458g	39	1	168	53	18.78	1	4.45	4.05	Pm	4.5	pm	0.45	150	83	84	119	80	
40	2112748g	37	1	165	65	23.88	2	7.3	11.5	Am	12.43	pm	0.53	100	65	80	78	59	60
41	9453147f	19	1	174	49	16.18	1	4	1.05	Pm	1.47	pm	0.42	100	92	71	77	75	
42	2413859g	41	1	156	58	23.83	2	6.3	1.3	Pm	2.1	pm	0.4	200	101	96	98	88	101
43	2406778g	31	1	168	54	19.13	1	2.3	3.1	Pm	3.35	pm	0.35	150	110	89	109	100	
44	5674432f	46	2	160	72	28.13	2	6	4.1	Pm	4.4	pm	0.3	140	101	94	101	74	92
45	0305359g	42	1	159	56	22.15	1	1.05	7.45	Am	8.1	am	0.35	160	84	89	98	82	
46	2514444g	48	1	165	65	23.88	2	4	12.4	Pm	13.55	pm	1.15	160	72	84	85	100	97

hrport	sbpprein	sbpind	sbpint	sbpperi	sbpbucc	sbpport	dbpprein	dbpind	dbpint	dbpperi	dbpbucc	dbpport	mappprein	mapind	mapint	mapperi	mapbucc
98	121	91	95	94		107	89	51	39	34		61	95	62	52	47	
105	152	142	173	124	129	157	91	88	105	77	79	101	108	100	120	89	91
102	139	92	107	90		157	83	62	69	57		93	96	69	78	65	
116	121	92	108	103		130	55	54	63	56		49	73	64	73	68	
106	135	77	130	97		106	87	51	70	59		48	100	56	85	68	
73	121	93	90	90		116	73	54	45	45		66	85	65	64	64	
92	99	99	155	80	49	130	73	73	111	55	49	81	78	78	122	61	58
85	103	95	142	102		102	58	62	83	57		57	68	67	97	68	
84	112	80	83	98	115	120	83	48	51	61	77	78	89	55	59	68	85
68	120	104	97	70	101	120	70	60	62	40	52	77	84	71	70	46	63
94	148	130	137	86		128	82	83	100	50		75	99	93	108	59	
78	142	76	174	106	121	118	68	59	105	60	64	68	88	63	119	72	78
93	149	106	113	98	93	142	76	84	60	41	40	83	93	90	71	54	52
85	128	123	124	113	111	130	67	83	73	68	63	70	81	90	85	78	75
95	113	97	84	103		82	63	55	46	58		37	75	64	55	70	
112	160	140	120	98	100	117	90	81	76	50	55	69	107	94	86	59	66
101	115	110	130	105	110	109	80	63	98	66	70	65	89	73	105	75	80
75	140	124	120	92	94	147	98	98	88	55	60	89	104	102	98	67	71
80	137	129	84	80		140	80	79	49	56		80	95	90	57	65	
86	135	130	100	95	115	120	84	80	60	58	64	70	96	103	77	64	78
101	121	135	163	112	120	119	79	82	80	64	61	70	88	94	98	75	76
78	131	119	119	98	96	110	82	83	85	48	50	60	96	92	92	62	60
84	108	119	112	103	118	120	77	81	89	59	70	72	83	90	94	69	82
88	123	112	89	99		115	80	75	55	56		76	91	84	62	72	
120	140	81	132	101	121	109	90	47	85	60	83	62	101	56	95	70	90
70	128	108	130	100	96	108	82	62	70	58	50	55	68	68	78	64	62
104	129	131	163	101	106	121	78	77	110	61	56	58	90	89	123	72	69
88	117	88	74	85	128	114	75	63	47	43	74	78	83	69	54	52	86
99	132	133	94	96	98	103	76	81	51	53	51	64	90	92	40	61	61
81	124	114	112	97	97	101	80	79	78	55	55	61	86	80	85	66	66
109	140	79	99	91	89	100	86	44	65	52	50	58	96	52	72	62	59
104	126	109	118	88		97	68	51	78	58		58	83	66	88	63	
71	125	68	114	109	119	126	78	39	67	53	59	80	89	47	78	65	71
87	114	87	90	102		107	75	50	60	67		67	84	57	67	73	
70	138	130	108	100	130	120	58	80	55	58	70	80	71	95	67	64	90
84	133	110	120	100	100	120	93	80	86	59	60	90	100	90	93	62	61
113	121	115	121	100		130	73	67	79	60		81	85	77	89	70	
124	143	109	103	89	115	114	83	73	62	47	64	81	97	82	69	57	75
104	115	86	76	104		135	59	42	45	56		73	71	52	52	67	
106	138	112	115	104	124	137	79	78	79	79	80	82	92	80	79	75	80
109	102	99	125	148		110	50	44	76	60		70	63	57	87	90	
114	164	117	118	90	113	130	101	67	68	58	61	73	123	71	84	65	66
95	110	105	108	88		109	69	64	66	50		53	77	74	75	59	
84	140	110	127	126	117	128	82	65	76	70	79	80	94	75	85	83	90

mappost	timeagen	timeagen1	timeextu	timeextu1	tbagsent	vsrec	var1	var2	var4	var6	var8	var12	var24	nsrec	nx1	nx2	nx4	nx6	nx8	nx12
100	6.4	pm	6.5	pm	0.1	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2
113	5.3	pm	5.45	pm	0.15	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2
107	6.06	pm	6.13	pm	0.07	0	0	2	2	2	4	4	4	2	2	2	2	2	2	2
66	3.1	pm	3.25	pm	0.15	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2
61	11.05	am	11.2	am	0.15	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2
77	7.15	pm	7.35	pm	0.2	0	0	0	0	2	4	4	4	2	2	2	2	2	2	2
93	4.15	pm	4.3	pm	0.15	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
68	1.13	pm	1.25	pm	0.12	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2
86	7.3	pm	7.45	pm	0.15	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2
90	5.25	pm	5.45	pm	0.2	0	0	0	0	0	2	3	4	3	3	3	3	2	2	2
86	2.2	pm	2.3	pm	0.1	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
79	7	pm	7.45	pm	0.45	0	0	0	2	4	4	5	6	1	2	2	2	2	2	2
96	6	pm	6.15	pm	0.15	0	0	0	0	2	2	4	4	2	2	2	2	2	2	2
85	4.15	pm	4.55	pm	0.45	0	0	0	0	0	0	0	0	4	2	2	2	2	2	2
48	3.5	pm	4	pm	0.1	0	0	0	0	0	2	3	3	3	3	3	2	2	2	2
82	5.1	pm	5.25	pm	0.15	0	0	0	0	0	2	4	4	3	2	2	2	2	2	2
77	10.53	am	11.1	am	0.17	0	0	0	0	0	0	3	4	2	2	2	2	2	2	2
104	6.56	pm	7.14	pm	0.18	0	0	0	0	2	4	6	6	2	2	2	2	2	2	2
97	9.47	am	10	am	0.13	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
80	4.15	pm	4.4	pm	0.25	0	0	0	0	0	2	2	3	2	2	2	2	2	2	2
81	4.5	pm	5.2	pm	0.3	0	0	0	0	2	2	4	4	2	2	2	2	2	2	2
68	6.1	pm	6.3	pm	0.2	0	0	0	0	0	4	4	4	2	2	2	2	2	2	2
81	11.55	am	12.05	pm	0.1	0	0	0	0	2	2	3	4	2	2	2	2	2	2	2
82	4.25	pm	4.3	pm	0.05	0	0	0	0	2	2	4	4	2	2	2	2	2	2	2
74	8.19	pm	9.01	pm	0.42	0	0	0	0	0	4	4	4	3	2	2	2	2	2	2
68	6.35	pm	6.48	pm	0.13	0	0	0	0	2	2	4	4	2	2	2	2	2	2	2
69	7.05	pm	7.3	pm	0.25	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2
84	8.4	pm	8.52	pm	0.12	0	0	0	0	0	0	2	2	3	3	3	3	2	2	2
79	7.4	pm	7.5	pm	0.1	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
74	12.4	pm	12.5	pm	0.1	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2
64	7.5	pm	8	pm	0.1	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2
63	4.15	pm	4.3	pm	0.15	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2
93	6.15	pm	6.3	pm	0.15	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
81	6	pm	6.2	pm	0.2	0	0	0	0	0	2	4	4	2	2	2	2	2	2	2
93	8.1	pm	8.15	pm	0.05	0	0	0	0	0	0	2	4	2	2	2	2	2	2	2
92	5.45	pm	5.55	pm	0.1	0	0	0	0	2	4	5	5	4	3	2	2	2	2	2
95	8.25	pm	8.4	pm	0.15	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2
90	6.3	pm	6.42	pm	0.12	0	0	0	4	5	8	6	6	2	2	2	2	2	2	2
88	5.36	pm	5.47	pm	0.11	0	0	0	0	2	6	6	4	2	2	2	2	2	2	2
85	7.15	pm	7.3	pm	0.15	0	0	0	0	0	4	6	4	2	2	2	2	2	2	2
85	5.3	pm	5.4	pm	0.1	0	0	0	0	0	0	0	2	2	2	2	2	2	2	2
74	9.1	pm	9.25	pm	0.15	0	0	0	0	0	0	2	2	2	2	2	2	2	2	2
74	9.05	am	9.15	am	0.1	0	0	0	0	0	2	2	2	2	2	2	2	2	2	2
86	4.27	pm	4.39	pm	0.12	0	0	0	0	4	5	5	4	2	2	2	2	2	2	2

ns24	ponvrec	ponv1	ponv2	ponv4	ponv6	ponv8	ponv12	ponv24	mouth	bvarec	bva1	bva2	bva4	bva6	bva8	bva12	bva24	tbeatfol	tbeatmob
2	0	0	0	0	0	0	0	0	2									17.1	15.1
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	2	6.15	5.45
2	0	0	0	0	0	0	0	0	2									6.17	17.17
2	0	0	0	0	0	0	0	0	2									8.05	18.35
2	0	0	0	0	0	0	0	0	2									6.4	20.4
2	0	0	0	0	0	0	0	0	2									5.25	14.55
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	4	4	8	22.3
2	1	1	1	1	2	2	0	0	2									6.35	18.35
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	2	6.15	17.15
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	2	2	14.15	17.15
2	2	2	2	0	0	0	0	0	2									7.3	17.3
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	4	4	5	5.15	14.45
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	7.45	15.15
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	4	4	5	6.05	14.05
2	0	0	0	0	1	0	0	0	2									3.3	16
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	2	3	3	5.35	13.35
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	3	5	5	2.5	20.5
2	0	0	0	0	0	0	0	0	1	0	0	0	2	4	4	4	4	5.46	22.16
2	0	1	0	0	0	0	0	0	2									3	20.3
2	0	0	0	0	0	0	0	0	1	0	0	0	2	4	4	4	4	5.2	15.2
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	4	4	4.4	15.1
2	1	0	0	0	0	0	0	0	1	0	0	0	0	0	4	4	4	3	16.3
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	2	3	3	4.55	19.55
2	0	0	0	0	0	0	0	0	2									5.3	15
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	4	4	4	6	12
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	2	4	4	6.12	12.12
2	0	0	0	0	0	0	0	0	1	0	0	0	2	4	4	2	2	12	14.3
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2	2	10.22	13.08
2	0	0	0	0	0	0	0	0	1	0	0	0	0	2	4	4	4	10.2	12.1
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2	2	5.1	18.1
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	10	24
2	0	0	0	0	0	0	0	0	2									5.3	15
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2	3	3.3	13.3
2	0	0	0	0	0	0	0	0	2									4.1	12.4
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2	2	9.45	20.15
2	0	1	1	0	0	0	0	0	1	0	0	0	2	4	4	4	4	11.05	22.05
2	0	0	0	0	0	0	0	0	2									2.2	10.2
2	0	0	0	0	0	0	0	0	1	0	0	0	4	4	3	3	3	4.18	22.18
2	0	0	0	0	0	0	0	0	2									4.13	13.13
2	2	2	2	2	2	2	2	2	1	0	0	0	0	0	2	2	2	4	20.3
2	0	0	1	0	0	0	0	0	2									2	24
2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	2	2	9	17.3
2	0	0	0	0	0	0	0	0	2									3.15	21.15
2	0	0	0	1	1	0	0	0	1	0	0	0	0	2	4	2	2	7.2	23.2